

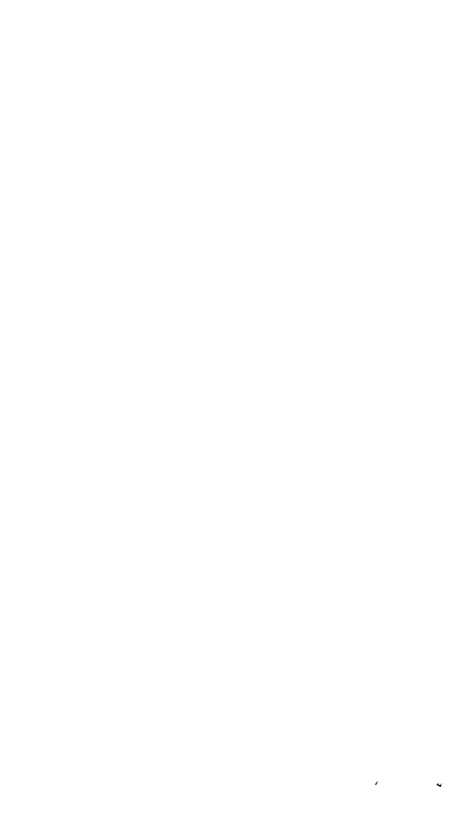


ESSENTIALS OF  
PHARMACOLOGY



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# Essentials of Pharmacology

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At the end of each chapter, there is a list of important preparations of the drugs discussed and a fairly extensive bibliography. The preparations are compiled from the Pharmacopoeia of the United States, Thirteenth Revision, 1947; from the British Pharmacopoeia, 1932, including Addenda I-VII; and from New and Nonofficial Remedies, 1947. We have followed the U.S.P. XIII usages of English names for drugs and the metric system for dosage. For practical pur-

Pharmacology has also built a place for itself in other professional fields such as dentistry, nursing, pharmacy and veterinary medicine. Furthermore, popular knowledge of this science is becoming more and more widespread as the result of such dramatic advances as insulin, the "sulfa" drugs, penicillin and the new antimalarial agents.

The first course in pharmacology in medical schools is usually given after preparation of the student in anatomy, bacteriology, biochemistry, physiology and pathology. Expert-materials and methods, turning to the clinical sciences for help in those researches requiring the use of human subjects. Pharmacology draws freely on all these sciences for its materials and methods, turning to the clinical sciences for help in those researches requiring the use of human subjects.

in the field.

This book is intended to serve as an introductory text in pharmacology. Much of the detailed documentary material necessary for the more advanced student or the research worker has been omitted, and scant mention has been made of such drugs as nicotine, strychnine and muscarine, which are of considerable importance from the viewpoint of pharmacodynamics but are little used in present-day medicine. On the other hand, the general principles of pharmacology have been stressed wherever possible, and efforts have been made to indicate what appear to be the coming trends in the field.

Preface

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poses, the references have been largely limited to recent articles, written in English and published in readily available journals.

We are grateful to a number of colleagues who have read and offered criticisms of various chapters. In particular we are indebted to Dr. M. E. Davis of the Department of Obstetrics and Gynecology, to Dr. J. G. Allen, Dr. A. S. Alving, Dr. E. B. Bay, Dr. A. T. Kenyon, Dr. C. P. Miller, Dr. W. L. Palmer, Dr. H. T. Ricketts, Dr. S. Rothman and Dr. C. L. Spurr of the Department of Medicine and Dr. W. H. Taliaferro of the Department of Bacteriology and Parasitology of the University of Chicago; to Dr. J. J. Jacoby of the Department of Surgery of Ohio State University and Dr. F. F. Snyder of the Department of Obstetrics and Gynecology of Harvard Medical School. We are also indebted to our associates in the Department of Pharmacology, Dr. J. M. Coon, Dr. K. P. Dubois and Dr. J. R. do Valle, Guggenheim Fellow in Pharmacology and Professor of Pharmacology at São Paulo University, Brazil, for many constructive suggestions. We also wish to acknowledge the invaluable assistance of Mr. Wallace Tourtellotte, Research Assistant in Pharmacology.

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# Historical Development of Pharmacology

## I

Pharmacology is a compound word derived from the Greek terms *pharmakon* meaning medicine or drug and *logos*, a discourse or study. The science of pharmacology has been defined by Schmiedeberg as "an experimental science which has for its purpose the study of changes brought about in living organisms by chemically acting substances (with the exception of foods) whether used for therapeutic purposes or not."

Modern experimental pharmacology is one of our newest disciplines, as far as university organization is concerned, yet it had its beginnings in antiquity. Ever since man's advent on earth, one of his main concerns has been the alleviation of pain and suffering, consequently, each succeeding period of history has had its own system of healing based, in part at least, on the scientific concepts of the time. Early man sought a reason for pain and for disease processes; he ascribed them to the presence of evil spirits or considered them as punishments from the gods for wrongs he had done. The first remedies, accordingly, were intended to drive away the evil spirit or to punish the individual for wrongs done and were chosen for their disagreeable taste or odor.

In ancient times, as today, much suffering and disease ran their course or came to spontaneous remission regardless of the therapy used. Such recoveries gave an apparent validity to many remedies that were actually worthless.



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quity. Freedom of thought and individual scientific effort had, by the seventeenth century, led to a curious anomaly. While medical science was progressing, popular medicine was retrogressing. The same century that saw the use of the royal touch to cure the king's evil, and the exploitation of many useless remedies also saw Harvey's epochal observation of the circulation of the blood and Malpighi's introduction of microscopic anatomy and the beginnings of animal experimentation.

These discoveries in the field of scientific medicine, together with the beginnings of modern chemistry and physics, formed the ferment out of which was to come modern experimental pharmacology. Throughout the eighteenth century men of science endeavored to classify and to correlate the new knowledge; it became the age of theories and systems. Théophile de Borden enunciated a theory of endocrine secretions, postulating that each organ serves as a factory for its specific humor, which is absorbed into the blood stream and carried to distant organs. William Withering introduced digitalis, after identifying it as the active ingredient in a recipe obtained from an old woman of Shropshire, thus establishing the rationale for another bit of successful folk-medicine.

The organized advancement of modern pharmacology began with the nineteenth century. With the development of organic chemistry, isolation and identification of the active principles of crude drugs became possible, among the earliest being the isolation of morphine by Serturner in 1804. Physiologic problems could now for the first time be approached from the standpoint of chemistry and physics, an approach which marked the end of vitalism. Understanding of the transmission of infection and of the bacteriologic nature of many diseases opened new fields for therapeutics. The introduction of anesthesia led to great and rapid progress in the clinical and experimental medical Up to 1850, the French were leaders in scientific medical

On the other hand, some substances employed by fortuitous circumstances were of specific value in certain diseases and are part of our armamentarium today. Among the multitudinous recipes listed in Eber's papyrus, an Egyptian record of 1550 B.C., are such drugs as castor oil, colchicum and opium, which are still in use.

In the Egyptian period and even in the early Greek period, medicine was a part of religion and philosophy. The concept of disease as a pathologic process going on within the body, rather than as a visitation from the gods, was formulated for the first time by Hippocrates (460-370 B.C.) and marks the beginnings of scientific medicine. Accurate observation of the course of illness made it possible to classify and appraise the use of drugs. Unfortunately, the scientific principles of Hippocrates were not to be fully carried out until the dawn of the Renaissance many centuries later. With the decline of Greek culture, the quest for fresh knowledge was forgotten. Although medicine among the early Romans was an honored and important field, under the influence of Galen (A.D. 131-201) it degenerated into a dogmatic system of polypharmacy. Instead of furthering observation and analysis of actual processes, Galen sought the answer to medical problems in pure theory. Throughout the late Roman and medieval periods, Galen's theories were accepted and medical progress ceased.

With the Renaissance, however, the Hippocratic spirit was revived. Free thought and critical inquiry led Paracelsus (1493-1541) to attack the Galenic system of polypharmacy. He introduced simplicity in prescription writing and recommended the use of chemical substances rather than the mixed vegetable preparations of Galen. The treatment of syphilis with mercurials was inaugurated by Paracelsus. The first official pharmacopoeia was printed in Florence in 1497.

The revolt against Galenic medicine did not, however, lead at once to the establishment of truly Hippocratic in-

progress. François Magendie studied the action of strychnine on dogs and made the first clear-cut scientific observation of the action of drugs on animals. Claude Bernard investigated carbon-monoxide poisoning and explained the mechanism of its action. Cavenou and Pelletier, pharmacists and skilled chemists, isolated as chemical entities such important alkaloids as strychnine, veratrine, brucine and quinine. The importance of toxicology as a branch of research was developed by Orfila, a Spaniard living in France. In the second half of the nineteenth century, the center of activity shifted to Germany with its two important schools of physiology—Johannes Müller's at Berlin and Ernst Weber's at Leipzig. Carl Binz, a pupil of Müller, became famous for his lectures on pharmacology and his fundamental work on cyanide poisoning and on quinine. Rudolph Buchheim, a pupil of Weber, established in the basement of his home the first laboratory of experimental pharmacology. His work so impressed the university authorities that he was invited to establish the first chair of pharmacology at the University of Dorpat in 1849, with adequate laboratory space in the Anatomical Institute.

Oswald Schmiedeberg was a pupil of both Buchheim and the well-known physiologist Carl Ludwig. Schmiedeberg, a man of robust constitution and indefatigable energy, who attracted students from all over the world is regarded as the founder of modern pharmacology.

The first full-time university professorship of pharmacology in the United States was created in 1890 at the University of Michigan and was held by John J. Abel. Victor G. Vaughan, the dean at the medical school at Ann Arbor, chose Abel to fill this position on the recommendation of Schmiedeberg. Vaughan, in his book "A Doctor's Memories,"\* tells the story of how Abel came to Michigan:



physical or chemical means. Such studies into the mechanism of drug action require, for example, the use of biochemical procedures for measurements of enzyme activity and the effects of drugs on the economy of the body; methods of physical chemistry are used for studies on dialysis, adsorption and diffusion of drugs; analytic and organic chemistry contribute methods for the analysis of biologic materials for drugs and drug metabolites; and finally nuclear physics has recently provided the very useful procedures of isotope-tracer techniques whereby the metabolism of a drug can be followed throughout its life in the body.

"When in 1890 we decided to have a real chair of pharmacology with laboratory instruction, I wrote to Professor Oswald Schmiedeberg, the dean of that science at that time in Strasbourg. He replied at length and advised me not to take a German, since he thought it a doubtful procedure to install a foreigner into a professorship. He said that he had in his laboratory two Americans, but that one of them was more German than American, and he recommended the other. Besides, he said that the man he was recommending was not only an American but a graduate of Michigan University. In this way John J. Abel became our first professor of pharmacology, as a real science." Thereafter in rapid succession, departments of pharmacology were established in many other universities in the United States.

Prior to Dr. Abel's appointment, materia medica and therapeutics were taught in this country by physicians engaged in private practice. Abel introduced Schmiedeberg's teaching methods, by lectures, demonstrations and discussions in pharmacology and by devoting considerable time to research. He further advanced the teaching of pharmacology by the inauguration of student experiments and by insisting on preliminary instruction in related departments in order that students would have a better background for their studies in pharmacology.

Early workers in the field of experimental pharmacology were limited to observation of responses to the action of drugs by living animals or by isolated organs and tissues. These methods remain of great importance in modern pharmacology for such procedures as biologic assay, the screening of new chemical compounds for their toxicity and possible therapeutic value and the isolation of pharmacologically active agents as chemical entities. In addition, technologic advances in the fundamental sciences have made possible more basic approaches through studies of enzymatic reactions which collectively make up the living cell and the enhancement or inhibition of these reactions by

complete evaluation. The literature is replete with instances in which immensely valuable compounds were well known for years before their pharmacologic action was discovered. The development of a theoretical background for pharmacology has now reached the point where it is possible at times to relate chemical structure to pharmacologic action and to predict with some success the activity of newly synthesized compounds. Certain series of compounds, notably the barbiturates, the local anesthetics and the sulfonamides, have been so thoroughly investigated that reasonably accurate predictions of the activity of a closely related analogue can be made from a consideration of its chemical structure. Even under the best of conditions, however, extensive animal experimentation is required before a drug can receive even limited trial in man.

## DRUG METABOLISM

Many of the quantitative and some of the qualitative differences in the pharmacologic action of two closely related drugs are due to differences in their metabolism in the body. Absorption, distribution in the various tissues and fluids of the body, persistence in the body, inactivation by adsorption, activation or inactivation by enzymatic change, and the rate and route of excretion are all factors which must be considered in the evaluation of any given drug. Such properties as diffusibility, solubility and degree of ionization of a drug may have a profound influence in determining the penetration or fixation of the drug by the cell, which, in turn, determines the efficiency with which it exerts its action.

Absorption. The factors controlling the rate and the extent of absorption of drugs are poorly understood. Solubility in water or in lipids is often but not always the determinant. The absorption of a drug may be strikingly different in different species of animals. For this reason it is highly desirable to use as many species as possible in study-



# General Principles of Pharmacology

SOURCES OF DRUGS  
DRUG METABOLISM

MECHANISM OF ACTION  
DETERMINATION OF TOXICITY

## SOURCES OF DRUGS

The discovery of the pharmacologic action or therapeutic usefulness of a substance can be made in several ways. The activity of most of the older drugs in our therapeutic armamentarium was found by pure chance. For the most part, the crude plant extracts formerly making up the majority of drug preparations have been subjected to study, and pure crystalline preparations have been obtained. As the composition of these purified substances is determined, new compounds with minor modifications in structure can be synthesized with a view to obtaining even better therapeutic agents.

Another approach is by the system introduced and practiced so successfully by the Germans of trying a large number of chemicals in a screening test designed to uncover a given pharmacologic activity. This procedure is responsible for the discovery of such widely used drugs as quinacrine, the sulfonamides and the arsenicals.

A third procedure is to undertake a deliberate methodical search for a medicinal use for a given preparation. However, the types of possible pharmacologic action are so varied, and the technics for determining activity so time-consuming and expensive, that few substances indeed have received

is referred to as "drug tolerance" and may be due either to a change in the rate of metabolism of the drug or a change in the reactivity of the cell involved. An increase in response is presumptive evidence that the rate of removal of the drug from the body (excretion plus detoxification) is less than the rate of administration, and is called "the cumulative effect." This phenomenon is distinct from that of "drug sensitization," which is characterized by the sudden appearance of toxic symptoms. These symptoms usually disappear promptly when the drug is discontinued, but may reappear with even very small doses.

## MECHANISMS OF ACTION

Drugs may exert their effects on a physical basis, e.g., the action of bismuth subcarbonate in coating the intestine to prevent irritation; or on a chemical basis, e.g., neutralization of gastric acidity by sodium bicarbonate. However, the majority of drugs are pharmacologically active by virtue of an interference with some enzymatic process essential to the normal economy of the affected cell. This interference may be either by an increase or by a decrease in the rate of a metabolic reaction. Enzymatic reactions are readily influenced by enzyme, substrate, and coenzyme concentrations, pH, temperature, and the presence of activators or inhibitors. Consequently, a drug affecting any of these factors may elicit a pharmacologic response. For example, cocaine and ephedrine inhibit the destruction of sympathin by combining with the enzyme *amine oxidase*; hence, certain of the pharmacologic effects of these two drugs can be attributed to the action of sympathin. Similarly, the action of physostigmine and the fluorophosphates is thought to be due to an inactivation of *choline esterase* by reversible and irreversible combination respectively, resulting in a prolongation of the effects of the acetylcholine liberated at the nerve endings.

Several chemotherapeutic agents have been shown to be

ing the absorption characteristics of new compounds. For most drugs there are one or more preferred routes of administration which give the desired intensity and duration of the response.

**Intermediary Metabolism.** The variation in the rate of the intermediary metabolism of a given drug in different species of animals may be even greater than the variation in absorption. Furthermore, the intermediate or end products of metabolism may be quite different in different animals, thus accounting, at least in part, for the variable response. Hence, investigative pharmacology requires a knowledge of the enzyme systems which may be involved in the metabolism of drugs.

For a drug to be effective it must reach the site of its action. The pattern of distribution of the drug in the tissues may vary from one species of animal to another. Pathologic or physiologic states may also effect the distribution and therefore the efficacy of a drug. Furthermore, the metabolic changes produced in a drug by the action of one or more of the many enzymes in the body may either increase or decrease its pharmacologic potency. Finally, a drug may be noneffective if combined as an adsorption complex with some normal constituent of the body such as serum or tissue proteins or bone.

**Excretion.** The rate of excretion of a drug from the body is important in determining the duration of its effect. In addition, the route of excretion often affords a convenient way to obtain a therapeutically useful localized concentration of the drug in the excretory channel. However, in some cases, toxicity may be partly dependent on the excretion characteristics of a given drug because of this concentration. Furthermore, pathologic changes in the excretory organ may markedly decrease tolerance to the drug.

**Drug Tolerance, Accumulation and Sensitization.** Repeated administration of a drug frequently is accompanied by either a decrease or an increase in its action. A decrease

is referred to as "drug tolerance" and may be due either to a change in the rate of metabolism of the drug or a change in the reactivity of the cell involved. An increase in response is presumptive evidence that the rate of removal of the drug from the body (excretion plus detoxification) is less than the rate of administration, and is called "the cumulative effect." This phenomenon is distinct from that of "drug sensitization," which is characterized by the sudden appearance of toxic symptoms. These symptoms usually disappear promptly when the drug is discontinued, but may reappear with even very small doses.

## MECHANISM OF ACTION

Drugs may exert their effects on a physical basis, e.g., the action of bismuth subcarbonate in coating the intestine to prevent irritation; or on a chemical basis, e.g., neutralization of gastric acidity by sodium bicarbonate. However, the majority of drugs are pharmacologically active by virtue of an interference with some enzymatic process essential to the normal economy of the affected cell. This interference may be either by an increase or by a decrease in the rate of a metabolic reaction. Enzymatic reactions are readily influenced by enzyme, substrate, and coenzyme concentrations, pH, temperature, and the presence of activators or inhibitors. Consequently, a drug affecting any of these factors may elicit a pharmacologic response. For example, cocaine and ephedrine inhibit the destruction of sympathin by combining with the enzyme *amine oxidase*; hence, certain of the pharmacologic effects of these two drugs can be attributed to the action of sympathin. Similarly, the action of physostigmine and the fluorophosphates is thought to be due to an inactivation of *choline esterase* by reversible and irreversible combination respectively, resulting in a prolongation of the effects of the acetylcholine liberated at the nerve endings.

Several chemotherapeutic agents have been shown to be

effective by virtue of a similarity to an essential metabolite of the invading organism, with a resultant competitive inhibition of reactions in which that metabolite is concerned. For example, the action of sulfanilamide can be completely neutralized by the presence of small additional amounts of the essential metabolite, para-aminobenzoic acid. Other sulfonamide drugs apparently interfere with the normal utilization of other metabolites as well, e.g., riboflavin, nicotinic acid and thiamine. Other examples of antagonism are desthiobiotin, which interferes with the utilization of biotin, pantoyletaurine with pantothenic acid, 6,7-dichlororiboflavin with riboflavin, and pyrithiamine with thiamine.

The principle of biochemical antagonism has recently been applied in the search for drugs other than chemotherapeutic agents. Examples of these include imidazole and derivatives which act as antihistamine substances, and pteroyltriglutamic acid, which interferes with pteroylglutamic-acid metabolism in tumor tissue.

Certain other drugs exert their action by supplying an essential constituent of the cell. Examples of this type of action are the vitamins, hormones and the essential minerals, amino acids and fatty acids. Synthetic compounds which can substitute for the natural ones in metabolic reactions are also included in this group, such as menadione, diethylstilbestrol and metacholine.

**Drug Combinations.** Formerly it was the custom to use medicines composed of a large number of supposedly active ingredients. This "polypharmacy" was perhaps inevitable in the past, but now drug combinations are only prescribed when there are specific indications. Two or more drugs when used together may have a *synergistic* or an *antagonistic* action. By synergistic action is meant the production of an effect which is more intense or more prolonged than would be obtained with either drug used alone. This term is also used in a more limited way to designate those instances in which the effect is more than additive, i.e., the

response is greater than the algebraic summation of the effects of the drugs when used alone. This latter definition also applies to the term *potentiation*. Synergistic action can be illustrated by the following drug combinations: morphine-scopolamine, procaine-epinephrine, sulfadiazine-sulfamerazine, pentaquine-quinine. Antagonistic actions can be illustrated by the following pairs of drugs: pentobarbital-picrotoxin, bromide-amphetamine, atropine-physostigmine, para-aminobenzoic acid-sulfonamide. Further details are given in the appropriate chapter of this text.

## DETERMINATION OF TOXICITY

Before attempting therapeutic use of a new drug, or of a new sample of a familiar drug of unknown purity obtained from natural or synthetic sources, it is necessary to know its toxicity. This property of a drug is usually expressed as "median lethal dose" or  $LD_{50}$ . It is the amount of drug per unit of body weight which, for a given species, will kill half the animals when administered to a group. When a drug is given by inhalation, this property may be expressed as  $LC_{50}$ , or the concentration of the drug in the inspired air, times the duration of exposure, which will kill 50 per cent of a group of animals. The rate and duration of administration and the species of animal used must be reported along with the numerical value obtained.

Individuals from any strain, no matter how carefully bred, may differ in their resistance to a drug. The various personal susceptibilities or "individual lethal doses" are so distributed in any population that their logarithms fall on the normal bell-shaped frequency or error curve. As a result, if varying doses of a drug are given to groups of animals and the log dose is plotted against per cent mortality, the latter on the "probability scale" of special probability coordinate paper, the points fall roughly on a straight line. The intersection of this line with the 50 per cent mortality ordinate gives the logarithm of  $LD_{50}$ .

Owing to the variation between individuals, it is necessary to use a reasonably large number of animals in each group. Five groups of twenty or thirty animals should be sufficient for determining the  $LD_{50}$  of an unknown drug. The approximate toxicity must, of course, be determined by preliminary observations on smaller groups and doses for the assay, so chosen that mortalities near 0 or 100 per cent are avoided.

Analysis of the potential toxicity of a drug requires its administration in both short-term (acute) and long-term (chronic) experiments. Acute-toxicity experiments are of considerable value in the rough "screening" of large numbers of new, closely related drugs, in order to select the most promising one for the more elaborate and more costly chronic-toxicity studies. These latter are necessary because of the frequent cumulative action of drugs, and because of the possibility of a delayed toxic action, when histologically or functionally undetectable damage may result in a major breakdown of some organ or function long after the drug has been discontinued.

### BIBLIOGRAPHY

- Bernheim, F.: *The Interaction of Drugs and Cell Catalysts*, Minneapolis, Burgess, 1946.
- Clark, A. J.: *The Mode of Action of Drugs on Cells*, Baltimore, Williams & Wilkins, 1935.
- Clark, A. J.: *General Pharmacology*—Supplement IV to Heffter's *Handbuch der experimentellen Pharmakologie*, Berlin, Springer, 1937.
- Gold, H.: *Cornell Conferences on Therapy*, New York, Macmillan, 1946.
- Green, D.: *Currents in Biochemical Research*, New York, Interscience, 1946.
- Gunn, J. A.: Cellular immunity: congenital and acquired tolerance to nonprotein substances, *Physiol. Rev.* 3:41, 1923.
- Hurst, H.: Biophysical factors in drug action, *Brit. M. Bull.* 3:132, 1945.

- Shaw, F. H.: The approach to therapeutics through the mode of action of drugs on cells. *M. J. Australia* 32: 649, 1945.
- Smith, A.: Medical Research—A Symposium, Philadelphia, Lippincott, 1946.
- Woolley, D. W.: Recent advances in the study of biological competition between structurally related compounds, *Physiol. Rev.* 27: 308, 1947.
- VanWinkle, W., R. P. Herwick, H. O. Calvery and A. Smith: Laboratory and clinical appraisal of new drugs, *J.A.M.A.* 126: 958, 1944.



### 3

# Control and Dispensing of Drugs

INTRODUCTION

PHARMACOPOEIAS, ETC.

LAWS AND REGULATORY  
AGENCIES

DRUG ASSAY

PRESCRIPTION WRITING

## INTRODUCTION

The safe use of pharmacologic agents is a practical problem involving the co-operation of several groups of individuals. Because of this divided responsibility, certain generally accepted practices and official rules of procedure have been evolved. Before a new drug can be sold on the open market, it must be subjected to adequate experimentation, not only in regard to its activity and possible therapeutic advantages but more particularly to its toxicity and potentiality for producing more harm than good. In addition, the manufacture and distribution of all drugs must receive some degree of public control in order to insure the reliability and uniformity of the final product. This chapter includes a discussion of the official standards for drugs, the laws governing them and the agencies for enforcement of these laws, a consideration of the problems of drug assay and a short presentation of the essentials of prescription writing.

## PHARMACOPOEIAS AND OTHER REFERENCES

The Pharmacopoeia of the United States of America (U.S.P.) was first published in 1820. The thirteenth edition became official on April 1, 1947. Since the passage of the

Food and Drug Act of 1906, the Pharmacopoeia has been recognized in courts of law as being the ultimate standard of reference for those drugs that are listed in it. The monograph on each drug includes a description of its chemical and physical properties; chemical or biologic tests for its identification, quality and purity, with stated limits of the amount of contamination with inactive or toxic substances; and the size of an average single dose for an adult. For practical reasons, only those drugs are included that are of therapeutic usefulness or pharmaceutical necessity and that are more or less widely used in medical practice within the United States or its possessions. Listing is restricted to active principles rather than mixtures or complex preparations. English names for drugs and the metric system for dosages are given preference over Latin names and the apothecaries' system.

The National Formulary (N.F.) was first published in 1888, 68 years after the appearance of the first edition of the U.S.P. It is currently in its eighth edition, which became official on April 1, 1947. The N.F. is compiled by the American Pharmaceutical Association and has as its purpose the function of serving as a "steppingstone" to and from the U.S.P. for those drugs which are not used widely enough to be included in the U.S.P. but which nevertheless are in some demand in certain sections and especially if they are listed in foreign pharmacopoeias or have been listed in the U.S.P. Furthermore, to increase the usefulness of the book, elixirs, fluidextracts, solutions, syrups, tinctures, pills, emulsions, mixtures and powders, and preparations belonging to the so-called "elegant pharmacy" are included. Originally, this compilation had no legal standing, but the Food and Drug Act of 1906 and the Food, Drug and Cosmetic Act of 1938 give both the National Formulary and the United States Pharmacopoeia the same official position. The British Pharmacopoeia (B.P.) was first published in London in 1864. It is currently in its sixth edition (1932)

with seven supplements covering changes in later years. It is in statutory force in most parts of the British Empire.

The United States Dispensatory (U.S.D.) was first published in 1833. It is a privately owned, nonofficial compilation and includes all items in the U.S.P., the N.F., and the B.P., as well as many nonofficial drugs less frequently used. At the time the U.S.D. was first published, the U.S.P. had been in existence for 13 years but had received almost no acceptance by the medical or pharmaceutical professions. Furthermore, the U.S.P. had at that time no legal standing and the U.S.D. was considered by far the more useful book, since it contained information on many more drugs. It is now in its twenty-fourth edition. Somewhat comparable volumes are the English Martindale's Extra Pharmacopoeia and the German Gehe's Codex.

New and Nonofficial Remedies (N.N.R.) is an annual publication of the Council on Pharmacy and Chemistry of the American Medical Association. The "New and Nonofficial Remedies" has no legal standing but items are submitted to the Council for consideration and if their standards are met, the item is "accepted." Products and accepted only so long as they conform to the standards of the Council both with reference to the quality of the product and the claims made for it in advertising by the manufacturer. No advertising in any of the American Medical Association's journals is permitted for nonaccepted items.

Accepted Dental Remedies (A.D.R.) is the publication, comparable to the N.N.R., compiled by the Council on Dental Therapeutics of the American Dental Association. Like the N.N.R., it accepts items on condition of maintenance of quality by the manufacturer and restriction of the advertising material to adequate and reasonable statements.

## LAWS AND REGULATORY AGENCIES

Prior to the passage of the Virus, Serum and Toxin Act of 1902 and the Food and Drug Act of 1906, there were

practically no restrictions on the manufacture or sale of medicinal products in the United States. In 1906 the first Drug and Cosmetic Act of 1938. This act prohibits the movement in interstate commerce of adulterated and misbranded food, drugs, devices and cosmetics. It has been of inestimable value in protecting the American public and has contributed markedly to the improvement of the quality and honest labeling of the nation's foods, drugs and cosmetics. The Food and Drug Administration is charged with the responsibility of enforcing the provisions of the act. This Federal agency also enforces the Caustic Poison Act of 1927, which safeguards the distribution and sale of certain dangerous caustic or corrosive acids, alkalis and other substances in interstate and foreign commerce. This act names twelve materials which are classified as dangerous, caustic or corrosive substances.

The Wheeler-Lea Act of 1938 is concerned mainly with the prevention of unfair trade practices involving the use of misleading or extravagant claims in advertising and is administered by the Federal Trade Commission, which co-operates with the Food and Drug Administration. The United States Post Office has the power to prosecute firms and individuals for fraudulent use of the United States mails.

The United States Public Health Service administers the Virus, Serum and Toxin Act of 1902. This act provides for the maintenance of potency and purity of biologic products. Licensing power is vested in this agency. The Harrison Narcotic Law of 1914, with subsequent amendments, regulates the importation, manufacture, production, compounding, sale, dispensing and giving away of opium or coca leaves or any compounds or preparations thereof. The Marihuana Act of 1937 regulates the importation, manufacture, production, compounding, sale, dealing

ing in, dispensing, prescribing, administering and giving away of marihuana. Both of these acts are enforced by the Bureau of Narcotics of the United States Treasury Department.

### DRUG ASSAY

The determination of the relative purity of a drug sample has a different purpose from the determination of the relative purity of ordinary chemicals. This purpose is bound up with the use to which the drug is put. Not only must it not contain toxic contaminants, but it must possess the therapeutic activity of the drug even in those instances in which nothing is known about the actual chemistry of the one or more compounds and the proportion of each which must be present in order for the drug to exert this therapeutic effect.

**Synthetic Chemicals.** For the most part, these drugs can be identified with sufficient precision and specificity. However, occasionally the compound is of such a nature that highly toxic substances may be formed during manufacture or storage. In such cases a simple test may be devised to detect such contaminants. For example, every package of tribromoethanol solution (avertin) is accompanied by apparatus and chemicals to detect the presence of hydrobromic acid in the product. If this test is positive, the drug must be discarded since it is proof that sufficient decomposition has occurred to make the use of the preparation undesirable.

The complex nature of some synthetic drugs makes it economically unsound to insist on chemical purity, yet the possible contaminants may be much more toxic than is permissible. Thus, in the case of the arsphenamines and arsenoxides, *only government licensees may manufacture the drugs*, and all lots must go through the hands of the National Institute of Health, where the toxicity is assayed on rats and the "expiration date" (the date beyond which the contents cannot be expected, beyond reasonable doubt, to retain stability) clearly printed on the package.

**Drugs of Plant or Animal Origin.** If the active components of the crude drug have been isolated and identified, the problem of assay is usually relatively simple. If they have not been identified, however, or if chemical-assay procedures are impractical, recourse must be had to biologic assay (bioassay), in which the drug sample is compared quantitatively with a standardized preparation of the same drug with regard to a particular pharmacologic effect. The strength or activity of the standard preparation is generally fixed by agreement among workers or by law. In a few cases, such as parathyroid hormone and antipernicious-anemia preparations, standard preparations are not available and the strength is determined by the amount of material required to elicit a certain pharmacologic response. The advantages of a standard preparation include a reduction in inaccuracies due to variations in animal susceptibility and to differences in the techniques of the assayists.

**Official U.S.P. Methods of Biologic Assay.** A few of these procedures are given in abbreviated form as illustrations of the principles of biologic assay. Strict observance of details, many of which are not repeated here, is usually necessary to obtain a valid assay.

**1. Tincture of Digitalis.** The amount of a diluted tincture of unknown potency required to kill etherized cats when injected intravenously is compared with the biologically equivalent amount of a standard tincture prepared from the U.S.P. Reference Standard. At least six cats must be used with each preparation, the injections should be made at 5-minute intervals and the dose should be such that between 13 and 19 injections are required to cause cardiac arrest. An error of 20 per cent is permissible. One U.S.P. digitalis unit represents the potency of 0.1 gram of the U.S.P. Reference Standard.

**2. Insulin Injection.** The blood-sugar-lowering effects of the unknown solution and of a standard solution are compared, using rabbits as the test animals. Groups of three

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ical and hematopoietic response in Addisonian pernicious anemia when administered daily.

## PRESCRIPTION WRITING

A prescription is an order for a medicine written by a physician and given to his patient. It is to be filled by a pharmacist. The physician is legally responsible for any errors but the pharmacist is co-responsible if a prescription is filled for a fatal dose of a drug. Prescriptions are necessary because of the great variety of therapeutic agents and because of the necessity for individual treatment. The size of the individual dose, the frequency of administration, the length of treatment and the form or vehicle in which the drug is given, as well as the actual composition of the medicine, will vary from patient to patient.

There is an increasing amount of governmental restriction on the dispensing of drugs and specific rules must be followed, especially in the prescribing of narcotics. In these instances, the prescription must contain the name, address and age of the patient as well as the physician's full name and his narcotic license number. When unusual amounts of narcotic are prescribed, justification must also appear on the prescription.

In writing a prescription, the prescriber should keep in mind the number of days the medicine will be taken, the total daily dose, the size of the individual dose, the stability of the drug, the cost, the sizes of standard containers and available dosage forms, and pharmaceutical (physical), chemical and therapeutic (pharmacologic) incompatibilities. A prescription contains the date and usually the name; address and age of the patient; the *superscription*, usually written as Rx, an abbreviation of "recipe" meaning "take thou"; the *inscription*, or body of the prescription, consisting of the name and the amounts of the *basis* (primary active drug), the *adjuvant* (secondary active drug, if any), the *corrective* (an agent to counteract some of the undesir-



rabbits each are used for three concentrations of both the unknown and the standard. Three analyses are done at intervals after the injection and the average depression of blood sugar used for the calculations. In order to minimize the effect of animal variation, the procedure must be repeated with the same rabbits several days later. The rabbits used in the first part of the assay for the standard preparation must be used in the second part for the unknown, and vice versa. The standard solution is prepared from the U.S.P. Zinc-Insulin-Crystals Reference Standard, the potency of which is 22 units per milligram. The concentration of the final solutions are adjusted so as to contain 40, 80 or 100 U.S.P. insulin units, with a variation of 5 per cent or less.

3. POSTERIOR-PITUITARY INJECTION. Dilute acetic-acid extracts of cleaned, dried and powdered posterior lobes obtained from the pituitary body of cattle or swine are compared with extracts of the Reference Standard. Suitable dilutions of the unknown and the standard extracts are added alternately to a special saline bath in which is suspended one horn of a virgin guinea-pig uterus. The contractions produced by both solutions must be approximately equivalent and submaximal. One U.S.P. unit is the amount of activity contained in 0.5 mg. of the U.S.P. Posterior Pituitary Reference Standard. A variation of 20 per cent is permissible.

4. LIVER EXTRACT. There is no satisfactory method for the biologic assay in animals of liver, stomach or other preparations intended for the treatment of Addisonian pernicious anemia. The products available are specifically approved by the U.S.P. *Antianemia Preparations* Advisory Board. Details concerning the source, the method of manufacture, etc., and clinical data from the treatment of susceptible human patients in relapse must be supplied. One U.S.P. unit is defined as that amount of an otherwise acceptable product which will produce a satisfactory clin-



# Administration of Drugs

INTRODUCTION	ORAL ADMINISTRATION	PARENTERAL ADMINISTRATION
	INHALATION	LOCAL APPLICATION
		RECTAL ADMINISTRATION

## INTRODUCTION

The pharmacologic activity of drugs is often profoundly influenced by the route, rate, duration and frequency of administration, and by such factors as the age, weight, sex, race and temperament of the subject. Various pathologic states and certain physiologic states, such as menstruation, pregnancy and lactation, may affect the absorption, intermediary metabolism or excretion of a given drug and thus necessitate giving special consideration to the dosage schedule.

The selection of the proper dose of a given drug for children is usually made with the aid of one of the several formulas which have been developed for the purpose. These are to be considered only as a general guide, not as inflexible rules. The ones in most common use are:

### Clark's Rule.

$$\text{Dose for child} = \frac{\text{weight of child}}{150} \times \text{dose for adult.}$$

### Cowling's Law.

$$\text{Dose for child} = \frac{\text{age at next birthday}}{24} \times \text{dose for adult.}$$

### Bush's Law.

$$\text{Dose for child} = \frac{\text{age} \times 5}{100} \times \text{dose for adult.}$$

able side actions of the other drugs, if any), and the *vehicle* (medium in which the other agents are dispensed); the *subscription*, or directions to the pharmacist regarding the preparation of the medicine; the *signatura*, or order to the pharmacist to label the medicine with the instructions for its use which follow. Finally, the prescription must be signed by the prescriber. It is common practice to have forms with the physician's name, address and office hours.

Formerly, all prescriptions were written in Latin with the apothecaries' system of weights and measures. The trend towards the more convenient use of English terms and the metric system is well illustrated by their adoption in the 1947 editions of the United States Pharmacopoeia, the National Formulary, and New and Nonofficial Remedies.

A description of certain pharmaceutic preparations and dosage forms is presented in Chapter 4.

### BIBLIOGRAPHY

de Beer, E. J.: The calculation of biological assay results by graphic methods—the all-or-none type of response, *J. Pharmacol. & Exper. Therap.* 85: 1, 1945.

Burn, J. H.: Biological Standardization, London, Oxford Univ. Press, 1937; Philadelphia, Blakiston, 1940.

Eggleston, C.: Essentials of Prescription Writing, Philadelphia, Saunders, 1942.

Green, F. H. K.: Clinical evaluation of new remedies in Britain, *Brit. Med. Bull.* 2: 58, 1944.

Herrick, A. D.: New Drugs, New York, Revere Publishing Company, 1946.

Lyman, R. A.: American Pharmacy. Volumes I and II, Philadelphia, Lippincott.

New and Nonofficial Remedies. Published Annually. Philadelphia, Lippincott.

Solomon, C.: Prescription Writing and Formulary, Philadelphia, Lippincott, 1935.

United States Dispensatory, 24th ed., 1947, Philadelphia, Lippincott.

Waud, R. A.: The use of Latin and the metric system in prescription writing, *Canad. M. A. J.* 56: 605, 1947.

Tinctures are alcoholic or aqueous alcoholic extracts of

Fluidextracts are concentrated liquid extracts of drugs. In all cases, the amount of active ingredient in 1 cc. is equivalent to the amount in 1 gram of crude drug. Alcohol is invariably present either to aid in the extraction or to act as a preservative.

Pills are globular or ovoid dosage forms of dry preparations intended for oral administration. They are made with a moistening agent or excipient, usually liquid glucose or syrup. Pills are generally coated to keep them from sticking together and to improve their appearance.

Troches are solid preparations, usually with a candy or glycerogelatin base, intended to be allowed to disintegrate slowly when placed in the mouth.

Tablets are molded or compressed solid medicinal substances, usually with lactose or lactose and sucrose as the base and alcohol or alcohol-water as the excipient. They may or may not be coated.

Enteric Coating. Pills and tablets may be given a special type of coating which is resistant to the gastric juices but which dissolves more or less readily in the intestinal tract. This is of special advantage for those drugs which are destroyed in the stomach or which produce undesirable local effects in the stomach.

The chief advantage of oral administration is its convenience. The action of practically all drugs is slower and more variable when they are given by mouth than when they are given by other routes. Many drugs cannot be effectively used by mouth because of their instability in, or poor absorption from, the gastro-intestinal tract, because their pharmacologic action is too fleeting or because the desired effect can be achieved by a distribution of the drugs in the body obtainable only by some other route of administration. The absorption of drugs given by mouth may also be affected by the presence or absence of food or alcohol.

**Young's Law.**

$$\text{Dose for child} = \frac{\text{age}}{\text{age} + 12} \times \text{dose for adult.}$$

The choice of the dose and the route of administration for a drug in a particular circumstance depend on the properties of the drug in question and the type of response desired. All other things being equal, the oral route is the method of choice. However, since some drugs are destroyed in the gastro-intestinal tract, and others are not absorbed or do not penetrate to the site of action, alternate routes are essential. The advantages and disadvantages of the various routes of administration are dealt with in this chapter.

**ORAL ADMINISTRATION**

A large variety of pharmaceutical preparations are available for the dispensing of drugs intended for oral administration.

Aromatic waters are saturated aqueous solutions of volatile oils or other aromatic or volatile substances. They have no therapeutic action since the concentration of the active ingredient is very low. They are used as flavored vehicles for water-soluble drugs, usually diluted with at least an equal volume of water.

Syrups are nearly saturated aqueous solutions of sugar, with or without flavoring agents. Alcoholic solutions of water-insoluble drugs may be added to syrups. Their chief use is as a vehicle for flavoring agents.

Infusions are aqueous extractions of crude drugs of animal or vegetable origin. Decoctions are similar except that they are prepared by extraction with boiling water.

Spirits are solutions of volatile substances in alcohol.

Elixirs are sweetened aqueous solutions containing flavoring materials and from 4 to 40 per cent alcohol. The alcohol content is just sufficient to keep the volatile oils or the medicinal agent in solution. The sugar content of elixirs is lower than that of syrups.

Vinegars are dilute acetic-acid extracts of crude drugs.

more certain effects than the oral or rectal route, with more exact dosage-response relations.

Solutions of drugs for parenteral use must be made with a pyrogen-free vehicle. Pyrogens are substances capable of causing a rise in body temperature. Pyrogens of bacterial origin may be found as contaminants of sterile distilled water. They are not destroyed by autoclaving and may be formed as a result of bacterial contamination of the still or distillate prior to the sterilization process. An official procedure for the demonstration of the absence of pyrogens in solutions intended for parenteral injection is described in the United States Pharmacopoeia. Three rabbits are used, 10 cc./Kg. of the solution to be tested are injected intravenously into each, and the subsequent body-temperature rise must not exceed  $0.6^{\circ}\text{C}$ . in any animal or a total of  $1.4^{\circ}\text{C}$ . for all three animals.

Parenteral solutions should be sterile whenever possible and must be given with aseptic precautions. This frequently necessitates the use of trained personnel and is one of the disadvantages of this route of administration.

Subcutaneous injections are made under the skin into the subcutaneous fat. The drug enters the blood stream fairly rapidly by diffusion through the capillary walls. Massage significantly accelerates the rate of absorption. The rate of absorption may be decreased by the inclusion in the injected solution of a vasoconstrictor, such as epinephrine. Irritant drugs cannot be administered subcutaneously because of the danger of sterile abscess formation and sloughing. This route is suitable for the injection of potent, nonirritating drugs, such as morphine, atropine and ergonovine.

Intradermal (intracutaneous) injections are used for producing regional anesthesia of the skin, for the administration of smallpox vaccine, and for diagnostic skin reactions. The agent is introduced between the layers of

the digestive enzymes and hydrochloric acid or bile salts in the gastro-intestinal tract. Furthermore, oral administration is sometimes obviously impracticable, as with moribund or unco-operative patients.

Drugs given by mouth generally pass through the liver by way of the portal circulation before entering the systemic circulation. Other routes of administration, including the rectal to a more or less variable degree, result in a direct absorption into the systemic circulation. Since many drugs are either destroyed or temporarily stored in the liver, this by-passing may result in a greatly increased sensitivity to a given amount of a drug. Consequently, the dose for oral administration may be much higher than for other routes of administration.

### RECTAL ADMINISTRATION

The rectal route is useful for local or for systemic administration as a supplement or alternative to the oral route when a drug cannot be given by mouth because the patient is unable to swallow or to retain oral preparations. Drugs may be given as suppositories or as retention enemas. In the latter case, the volume should be kept as low as is consistent with the irritant qualities of the more concentrated solutions. Certain drugs, such as tribromoethanol and ether-in-oil, are regularly given by this route; the salicylates, caffeine, morphine, mercurial diuretics and digitalis have been so administered but other routes are generally preferred. As supportive measures, saline and glucose solutions are often given by rectum. The chief disadvantages are that the procedure is unesthetic and liable to result in proctitis. Many drugs cannot be given in this way because of their irritant local action.

### PARENTERAL ADMINISTRATION

Parenteral administration is the administration of drugs under one or more layers of the skin or mucous membranes. In general, it offers the advantage of securing quicker and

Intra-arterial injections are rarely used except for diagnostic purposes. Subarachnoid (intrathecal, intraspinal) injections may be used for obtaining high local concentration of a drug as in the treatment of infections of the central nervous system or for the production of spinal anesthesia.

## INHALATION

Drugs are rapidly taken up by the blood stream through the pulmonary epithelium. Amyl nitrite and the volatile anesthetics are examples of volatile drugs commonly used by inhalation. Recently, techniques have been evolved whereby solid drugs can be dispersed in air in particles of a suitable size. If the droplet of drug solution, as in an aerosol, or the speck of solid drug, as in a smoke, is larger than 5 microns, the particle will usually be filtered out by the nose and throat. If it is smaller than 0.3 micron, it will usually be exhaled rather than fixed on the surface of the alveoli and absorbed. Because of this limitation, relatively precise apparatus is needed and this method has only limited application. It has been applied with variable success for the administration of the sulfonamides and the antibiotics and for drugs used in the treatment of asthma. It offers few, if any, advantages over intravenous therapy, since absorption is almost instantaneous.

## LOCAL APPLICATION

Drugs may be applied directly to the skin or to mucous membranes. For the application of drugs to the skin, the vehicle and method of application are often more important than the drug used.

Aqueous solutions are useful in the treatment of acute inflammation of the skin, where oozing and crusting occur following the damage to the capillaries. These solutions are applied as "dermatologic wet dressings." A wetted linen cloth is applied to the area and the cooling effect, produced



**Intramuscular injections** are suitable for aqueous solutions as well as for insoluble or immiscible preparations. In general, the rate of absorption is intermediate between that of oral administration and intravenous injection. In order to obtain an unusually slow rate of absorption, the drug may be given dissolved in peanut oil or beeswax or combined with a nonantigenic protein, such as protamine. Absorption can also be slowed by the inclusion of a vasoconstrictor in the solution to be injected or by the local application of cold packs.

**Intravenous injection** is the most rapid method of introducing drugs into the blood stream. Only drugs which do not precipitate in the blood can be used. Fairly irritant preparations can be given because of the rapid dilution by the blood. Precautions must be taken, however, to prevent leakage of such solutions around the venipuncture into the subcutaneous tissue.

**Intraperitoneal injections** are used in laboratory animals but seldom in human patients. The danger of puncturing the intestine or other viscera is slight but absorption is irregular, particularly if the circulation is impaired. Furthermore, irritant drugs may produce peritoneal adhesions.

**Intramedullary Injections.** Drugs injected into the bone-marrow spaces are taken up in the circulation about as rapidly as by intravenous injection. This route has also been used for the infusion of fluids. In adults, sternal puncture is preferred and, in infants, puncture of the femur or tibia. There is some danger of fat embolism, osteomyelitis or periostitis.

**Intracardiac Injections.** The heart can be entered readily by a sharp, direct thrust of the needle after first passing through one of the intercostal spaces. On a few rare occasions, the intracardiac injection of epinephrine has restored cardiac activity after complete standstill. Success in these cases was probably due as much or more to the mechanical stimulation of the puncture as to the drug.

Intra-arterial injections are rarely used except for diagnostic purposes. Subarachnoid (intrathecal, intraspinal) injections may be used for obtaining high local concentration of a drug as in the treatment of infections of the central nervous system or for the production of spinal anesthesia.

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by the evaporation of water, is sufficient to produce local vasoconstriction and so reduce inflammation. The cloth should, therefore, never be covered tightly as in a surgical wet dressing, and it should be replaced as soon as it is dry. The solution should be at room temperature in order to prevent reactive hyperemia. Usually it contains a mild antiseptic or an astringent agent.

Dusting powders are used for their moisture-absorbing effect. They should not be used in oozing dermatitis.

Lotions are aqueous solutions in which dusting powders are suspended. Addition of glycerol decreases the rate of evaporation of water and insures the formation of a continuous adherent layer of the powder after drying.

Ointments are greasy protective substances used as vehicles for drugs in subacute and chronic inflammatory processes. There are three groups of ointments: plain fatty substances of animal, vegetable or mineral origin, and oil-in-water and water-in-oil emulsions. Those of the first group are immiscible with water. Ointments of the second group contain emulsifying substances, such as wax, cetaceum or cholesterol or its derivatives and are miscible with water, forming stable emulsions. These emulsions are permeable to sweat and have some cooling effect due to a slow evaporation of water, as in "cold cream." They are used on inflamed, dry skin and also when aqueous solutions of drugs are to be incorporated into ointments. Oil-in-water (so-called greaseless bases) are rather unstable and their practicability is not established. Drugs incorporated in ointments usually penetrate into deeper layers of the skin than do those incorporated in the aqueous solutions, dusting powders or lotions. This is probably due to the partial suppression of insensible perspiration with accumulation of water in the skin and resultant maceration.

Pastes are mixtures of powders and ointments. Because of their powder content, they have a drying effect. They are less occlusive than ointments and therefore drugs :

incorporated into pastes act less intensively than if incorporated into ointments.

Plasters are solid preparations containing a mixture of rubber with solvents or diluents as a base. Medicaments incorporated into plasters penetrate deeply into the skin.

## SKIN

Few drugs are administered for systemic effects by application to the skin. Free mercury, when rubbed into hair follicles and sweat and sebaceous ducts is effectively absorbed. Fat-soluble hormones and vitamins have been shown to be appreciably absorbed through the skin. They are not ordinarily given in this way, however, except that occasionally testosterone is applied percutaneously in relatively high doses and estrogens have been applied by injection over mammary tissue. Salicylic-acid compounds have been applied percutaneously, and although there is some slight systemic absorption, the effects obtained are chiefly local. Fat-soluble compounds of toxicologic interest are known to be appreciably absorbed by percutaneous contact, e.g., phenol, nicotine and nitroglycerin.

Volatility and fat solubility are the two common characteristics which seem to determine percutaneous penetration. The horny layer of the epidermis (stratum corneum) is readily penetrated by nearly all substances since it is a sort of rough network of horny lamellae with large holes. The stratum granulosum and stratum lucidum represent the chief barrier to skin absorption. Such water-soluble inorganic substances as do penetrate the skin under special circumstances probably do so by entering the follicular and glandular pores. This type of penetration is favored by the concomitant use of substances which lower surface tension.

Galvanic currents can substantially increase the penetration of some ionizable drugs. The process is referred to as "electrophoresis" or "iontophoresis."

## ORAL MUCOSA

*Absorption through the stratified squamous epithelium under the tongue is largely conditioned by the fat-water distribution coefficient of a compound. Very few drugs have a high enough coefficient to penetrate directly through this mucosa. Glyceryl trinitrate and the steroid hormones, such as testosterone and desoxycorticosterone, have been effectively given in this way.*

## NASAL MUCOSA

*The columnar epithelium of the nasal mucosa is penetrated with reasonable ease. Pituitrin is occasionally given in this way during the management of diabetes insipidus. Immunization to tetanus and diphtheria has been accomplished clinically by this route.*

## OTHER MUCOSAE

*Drugs may be absorbed from the conjunctival sac, the vagina, the urethra or the bladder. These routes are not used, however, for the administration of systemically acting drugs, although occasionally systemic toxic reactions follow the application of drugs intended for local effects, e.g., atropine in the eye for pupillary dilation and ciliary muscle paralysis; mercury bichloride in the vagina as an ill-advised contraceptive measure; local anesthetics in the urethra. Drugs such as quinine and nicotine may be reabsorbed from the urinary passages, absorption being increased by an alkaline urine.*

## BIBLIOGRAPHY

Calvery, H. O., J. H. Draize and E. P. Lang: The metabolism and permeability of normal skin, *Physiol. Rev.* 26:495, 1946.

Draize, J. H., G. Woodard and H. O. Calvery: Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes, *J. Pharmacol. & Exper. Therap.* 82:377, 1944.

- Gaddum, J. H.: Principles of administration in chemotherapy, *Brit. M. Bull.* 4: 280, 1946.
- Hopkins, J. G.: Some newer bases for use in cutaneous therapy, *J. Invest. Dermat.* 7: 171, 1946.
- Lane, C. H., and I. H. Blank: Vehicles in topical dermatologic therapy: their functions and physicochemical characteristics, *Arch. Dermat. & Syph.* 54: 650, 1946.
- Loewey, F. E.: Histamine iontophoresis in general and industrial practice, *Brit. J. Phys. Med.* 8: 115, 1945.
- Mackee, G. M., M. B. Sulzberger, F. Herrmann and R. L. Baer: Histologic studies of percutaneous penetration with special reference to the effect of vehicles, *J. Invest. Dermat.* 6: 43, 1945.
- Mackenzie, J. W. A.: Absorption of drugs from the rectum, *Arch. Dis. Childhood* 17-18: 28, 1942-1943.
- MacQuigg, R. E.: New techniques for parenteral fluid and drug administration: I. Muscular intubation, *Surgery* 18: 592, 1945.
- Prigal, S. J.: The production of aerosols from medicated solutions, *J.A.M.A.* 131: 398, 1946.
- Quilligan, J. J., Jr., and H. Turkel: Bone marrow infusion and its complications, *Am. J. Dis. Child.* 71: 457, 1946.
- Rothman, S.: The principles of percutaneous absorption, *J. Lab. & Clin. Med.* 28: 1305, 1943.
- Schwidetsky, O.: History of needles and syringes, *Anesth. & Analg.* 23: 34, 1944.
- Tocantins, L. M., and J. F. O'Neill: Complications of intra-ossous therapy, *Ann. Surg.* 122: 266, 1945.
- Walton, R. P.: Sublingual administration of drugs, *J.A.M.A.* 124: 138, 1944.

# General Anesthesia

INTRODUCTION

RECTAL ANESTHESIA

INHALATION ANESTHESIA

CURARE

INTRAVENOUS ANESTHESIA

OXYGEN THERAPY

PREPARATIONS

## INTRODUCTION

The term anesthesia was coined in 1846 by Oliver Wendell Holmes to signify a state of "insensibility, more particularly . . . to objects of touch." The term may be used to describe either a general or a local effect. General anesthesia implies a loss of consciousness, a loss of pain sense (analgesia) and general muscular relaxation. These effects are produced by depression or narcosis of the central nervous system.

**Development of General Anesthesia.** The history of general anesthesia dates back to very ancient times. Such substances as mandragora, wines and other alcoholic preparations, opium, hyoscine (scopolamine) and cannabis (hashish, bhang, marihuana) were used to effect some loss of consciousness or analgesia for the crude surgery of ancient and medieval times. Stunning the patient, bilateral compression of the carotid arteries to produce cerebral anoxia and hypnotism or mesmerism were other procedures used in an attempt to induce some degree of anesthesia.

It was not until the advent of modern anesthesia in the middle of the nineteenth century, however, that the cries and struggles of the patient, with the resulting handicap to the surgeon during an operation, could be satisfactorily eliminated. The physicist, Sir Humphrey Davy, noted

early as 1800 that nitrous oxide would produce unconsciousness and abolish pain sense, but practical application of this agent in surgery was not made at that time.

Ether was first used as an anesthetic by Crawford W. Long in 1842, after he had observed that indigence in "ether frolics" to the point of intoxication would often result in loss of consciousness and abolition of pain sense. Shortly after this, a dentist, Morton, in Boston, upon the suggestion of his teacher, Jackson, tried ether to produce anesthesia during dental extractions and found it to be quite satisfactory. He was the first to give a successful public demonstration of the value of ether in general surgery, and from this time on the use of ether as an anesthetic became widespread. Previously, another dentist, Wells, had used nitrous oxide during dental extractions, but his attempted public demonstration of its value failed quite completely, and it was not until 1868 that nitrous oxide was introduced into clinical practice. Chloroform was first introduced as a general anesthetic by an Edinburgh obstetrician, James Simpson, in 1847.

The intravenous injection of drugs to produce general anesthesia was first used clinically in 1874 by Ore, who employed chloral hydrate. Although various other agents were tried, this method was considered too dangerous to attract widespread interest until the introduction of the ultra-short-acting barbiturates, hexobarbital and thiopental, in 1933 and 1934 respectively.

The rectal administration of drugs to produce general anesthesia was tried as early as 1847, using ether. This method was soon abandoned, however, because of irritation of the rectal mucosa. In 1913, Gwathmey reintroduced the technique of rectal anesthesia, using a nonirritating mixture of ether and olive oil. This became quite widely used, especially for obstetric analgesia. In 1926, tribromomethanol (avertin) was introduced for rectal anesthesia. It is now used almost solely as a basal anesthetic.



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while motor fibers are left free to conduct the negative charges away, thereby rendering the cortex electropositive.

## INHALATION ANESTHESIA

Administration. A number of gases and highly volatile liquids are used to produce general anesthesia. These are administered either by dropping the liquids on an appropriate mask which permits the inhalation of vapors or by the use of gas machines which deliver the gases and vapors into a face piece or an endotracheal tube. The early gas machines discharged the exhaled breath into the room air, a procedure now called the semiclosed method. New developments have made the so-called closed system more popular. In the closed system the exhaled breath passes into a gas reservoir, usually a rubber bag, and is rebreathed. The rebreathed gases pass through a canister containing soda lime, which removes the exhaled carbon dioxide. Oxygen is added at a rate of about 300 cc. per minute to replace that which is used up by the patient. This method permits the reuse of the exhaled anesthetic agent, thus effecting a considerable economy. It is more physiologic, since the inhaled gases are warmed and humidified. It also minimizes the dangers of anesthetic explosions and it provides a suitable apparatus for the administration of pure oxygen when necessary.

Stages of Anesthesia. The sequence of events following the administration of the various inhalation agents is qualitatively very similar and consists essentially of a gradually increasing depression of the central nervous system beginning with the higher cerebral centers. A number of characteristic signs occur during the administration of the anesthetic and reappear in reverse order as the anesthetic is withdrawn (see page 40). On the basis of these signs it is common to describe four stages of anesthesia, the first stage being one of analgesia, the second of excitement or delirium, the third of surgical anesthesia and the fourth

**Theories of Narcosis.** The mode of action of general anesthetics is not understood, although various theories have been advanced. The early belief was that anesthesia was caused merely by asphyxia. Claude Bernard was the first to suggest an alternate explanation, that anesthesia is due to a reversible coagulation of the constituents of the nerve cells. The Meyer-Overton theory assumes that the action of anesthetics is due to the fact that they are soluble in, and are taken up by, the lipids of nerve tissue, the anesthetic potency depending on the relative solubility of the agents in fats and water. The Moore and Roaf theory is an extension of the Meyer-Overton theory. It postulates that anesthesia is due to that part of the drug which leaves the lipids and combines with the protoplasm. The lipid material holds the anesthetic in contact with the protein and in this way aids in the production of narcosis. Recovery is due to the reversible nature of the combination of the narcotic with the cell protoplasm. According to Lillie's theory, anesthetics produce their effects by modifying cellular membranes, making them more resistant to changes of permeability. Since variations of permeability are essential to stimulation, the irritable tissue is thus rendered temporarily insensitive. Verworn's theory assumes that the depression of the neuron is due to suppression of the power of the cell to use oxygen, inasmuch as narcosis is accompanied by diminished oxygen utilization. Recent studies by Quastel on the effects of narcotics in decreasing the oxygen consumption of brain tissue *in vitro* have revived interest in this theory.

The administration of anesthetics causes a decrease in the electronegativity of the brain cortex so that in the stage of deep surgical anesthesia the brain cortex is electropositive. According to Burge's electrical theory of narcosis, the loss of negative potential is due to the blocking of the passage of negative charges into the cortex through sensory fibers,

















patient may have a sensation of choking or suffocation. If the agent is nonirritating, the patient may have pleasant flights of fancy and a sensation of giddiness, well-being and freedom from care.

Loss of consciousness ushers in the second stage of anesthesia. With skillful administration, this stage may be passed through uneventfully. Often, however, the patient exhibits signs of excitement or delirium, which vary from muttering and shouting, muscular tension and purposeless movements, to violent attempts to escape. There may be irregular breathing, breath-holding, coughing, salivation, swallowing movements, retching and vomiting. The blood pressure rises, the pulse accelerates, the pupils dilate and the eyes move about. There is exaggerated response to sensory stimuli, such that a loud noise, a touch or a movement of an extremity may precipitate a bout of violent activity.

During the first plane of the third stage, the respiration is full and rhythmic. The eyeball activity is greatest at the beginning of this plane but disappears by the time the second plane is reached. The pupils are usually normal but the eyelid reflex disappears. During the emergence from anesthesia, swallowing occurs at the upper border of the first plane of the third stage, while vomiting marks the lower limit of the second stage. The second plane is the one in which most surgical operations are performed. There is moderate muscular relaxation, and the general condition of the patient is good. The respiration remains unchanged and the pupils begin to dilate unless this reaction is modified by preanesthetic medication. The dilation may be due to a direct paralyzing effect of the anesthesia or to hypoxia. If morphine has been given, the pupils remain miotic until the third plane is reached. If scopolamine or atropine is given together with morphine, a mydriatic effect may predominate. In the third plane, respiration decreases in volume because of intercostal paralysis. The pupils become increasingly dilated even if morphine has been given, and the lacrimation

of respiratory paralysis, which leads to death unless appropriate resuscitative measures are taken. The anesthetist must be able to recognize the depth of anesthesia in order to insure that it is adequate for the surgical procedure in question and also to avoid the danger of giving an overdose of the anesthetic.

Signs of Anesthesia  
(After Guedel)

	Respi- ration Diaphrag- matic Thoracic	Eye- ball activ- ity	Pupils			Eye- lid Re- flex	Area of swal- low- ing	Area of vom- it- ing		
			No pre- anesthe- tic med- ication	With sco- pola- mine or atrop- ine	Alone					
1st Stage									Stage of analge- sia	
2nd Stage		+++							Stage of excitement	
3rd Stage		1	++++ +++ ++							Stage of surgi- cal anesthe- sia
		2					Most surgical procedures performed in this plane			
		3								
		4								
4th Stage									Stage of respiratory paral- ysis	

In the first stage of anesthesia, the patient is conscious but there is a variable degree of mental disorientation. Pain sensibility is diminished, so that this stage is often used in obstetric analgesia to provide relief during the intermittent labor pains. If the anesthetic agent is irritating, there may be coughing and voluntary breath-holding, and the

	ETHER	CHLOROFORM	NITROUS OXIDE	ETHYLENE	CYCLOPROPANE	VINYL ETHER
Toxicity Respiratory	Slow, deep in stage III. Apnea, when pushed. Respiratory failure late. Mucus obstruction. Laryngeal spasm.	Slow, deep in stage III. Resp. depressed.	Irregular and stimulated in III, partial asphyxial stimulation, then failure.	Normal resp. in stage II. Slow, reg., shallow like sleep. Asphyxial stim. if O <sub>2</sub> reduced.	Normal resp. and slowing in III. Apnea - when pushed - easily controlled by artificial respiration	Normal or slowed in III. Apnea - controlled with O <sub>2</sub> . Resp. failure before circulatory.
Resp. irritation	Salivation and mucus marked.	Little irritation.	No irritation.	No irritation.	Slight irritation	Mucus secretion. Marked salivation. Slight irritation
Circulation	B.P. normal in Stage III. Good circulation until late. Falls after resp. Cutaneous vessels dilated.	Vasomotor depression. Early fall in B.P. Myocardial damage and cardiac arrest	Asphyxial rise of B.P. in stage III. Circulatory failure secondary to asphyxia.	Slight drop in B.P. Slight bradycardia in III.	Little effect in stage III. Cardiac irregularities apt to occur	Myocardial damage in dogs
Stomach and gut	Relaxation marked	Relaxation very marked	Relaxation slight	Relaxation slight.	Relaxation slight	
Liver damage	Little or none	Delayed poisoning. Central necrosis	None	None	None	Less than with chloroform
Kidney	Little disturbance. Anuria and oliguria after prolonged use.	Anuria and oliguria earlier than with ether. Fatty infiltration and degeneration	None	None	None	
Postoperative nausea and vomiting	Frequent	Same as ether	A little	Present but much less than with ether	Present but less than with ether.	Small per cent
Operation for which suitable	Long - major	Brief or light anesthesia. Analgesia (obstet.)	Long in absence of anoxemia	Long - major - and induction	Long - major - and induction	Less than 1/2 - 1 hr.

TABLE 1  
CHARACTERISTICS OF THE MAIN INHALATION ANESTHETICS

	ETHER	CHLOROFORM	NITROUS OXIDE	ETHYLENE	CYCLOPROPANE	VINYL ETHER
Formula	$C_2H_5O$ $C_2H_5 > O$	$CHCl_3$	$N_2O$	$CH_2 = CH_2$	$\begin{array}{c} CH_3 \\   \\ CH_2 - CH_2 \end{array}$	$\begin{array}{c} CH_2 = CH \\   \quad \quad   \\ CH_2 = CH > O \end{array}$
Physical char. Sp. Gr. of vapor compared with air	Liq. b. p. 34.6° 2.56	Liq. b. p. 61° 4.10	Gas 1.52	Gas 0.90	Gas 1.45	Liq. b. p. 28° 2.42
Stability	Relatively stable	Unstable in light and heat.	Stable - in steel cylinders.	Stable - in steel cylinders.	Stable - in steel cylinders	Unstable after opening.
Inflammability	Inflammable and explosive	Noninflammable	Noninflammable. Supports combus- tion	Inflammable and explosive	Inflammable and explosive	Inflammable.
Administration	Inhalation— open semiclosed closed	Inhalation open closed	Inhalation— open semiclosed closed	Inhalation— open semiclosed closed	Inhalation—closed	Inhalation open closed
Anesthetic concentration	Induction 5-7% Maintenance 3.6%	Induction 1-2% Maintenance 0.5%	Induction 90% Maintenance 80-90%	Induction 80% Maintenance 70%	Maintenance 7½- 13%	Maintenance 4%
Induction Subjective	Slow 15-30 min. Warmth, giddi- ness, suffocation	Rapid 5-8 min. More pleasant than ether	Rapid 1-4 min. Exhalation	Rapid 3-8 min. Mildly unpleasant odor	Rapid 1-3 min. Pleasant	Rapid 2-3 min. Mildly unpleasant odor
Excitement	Present Resp. irregular Pupils dilated	Little excitement	Present, but passed over quickly	Uncommon	Uncommon	Little or none. Passed over quickly.
Surgical stage Muscular relax.	Excellent	Excellent	None	Poor	Good	Good
Oxygenation	Good - cyanosis late	Good	Poor	Poor	Good	Good

**Preoperative Preparation of the Patient.** The anesthetist should determine in advance the most suitable anesthetic agent and method for each patient, basing his selection on the physical condition of the patient and on the nature and duration of the operation. The patient should receive mental preparation in which his fears are allayed with reassurance and encouragement. He should receive adequate sedation on the night preceding the operation to permit restful sleep. About an hour before the operation he should be premedicated with such agents as morphine or related compounds to decrease metabolism and to allay pain and apprehension, barbiturates to produce sedation, atropine to reduce the bronchial and salivary secretions or scopolamine to reduce secretions and to produce amnesia. Basal narcosis may be produced with such agents as tribromoethanol or barbiturates. Basal narcosis or basal anesthesia is a condition of unconsciousness or very light anesthesia insufficient for surgical procedures. It is often induced before bringing the patient to the operating suite so that he is unaware of any of the events concerning his operation. It permits the maintenance of surgical anesthesia with smaller doses of anesthetic drugs than would ordinarily be required.

Postoperative measures include the administration of narcotics for severe pain, the use of intravenous fluids to combat dehydration and shock, the administration of antispasmodics to allay distention and oxygen therapy to prevent hypoxia.

### GENERAL ANESTHETIC AGENTS

Ether is probably the most widely used and safest general anesthetic. It produces a depth of anesthesia sufficient to give complete muscular relaxation while high concentrations of oxygen are maintained. Its disadvantages include the unpleasant and slow induction, irritation of the respiratory epithelium and high incidence of postoperative nausea and vomiting. If liquid ether is aspirated into the respiratory tract it is spilled in the eye, very severe irritation results.



reflex is abolished, giving a dull, lusterless appearance to the eyes. In the fourth plane, the respiratory volume is markedly decreased and the pupils are completely dilated. The intercostal muscles are paralyzed, and respiration is carried on entirely by diaphragmatic contractions, and is irregular and inefficient.

The depth of anesthesia depends on the concentration of anesthetic reaching the central nervous system. This is determined by the partial pressure of the anesthetic in the inspired air, the respiratory volume, the permeability of the alveolar membrane, the circulation time and the circulatory volume of the various organs and tissues.

*Desirable Properties of General Anesthetics.* Ideally, a general anesthetic should be a nonirritating substance free from any disagreeable odor. It should produce a rapid, pleasant induction and permit a rapid recovery. It should produce adequate muscular relaxation and should not increase capillary bleeding. It should have a wide margin of safety and be of adequate potency so that sufficient oxygen can be administered. It should be easy to administer and should cause little change in the normal physiology of the body. Finally, it should be easily and cheaply manufactured, nonexplosive and should not decompose on standing or during storage. The properties of the more important inhalation anesthetics are summarized in Table 1.

**Anesthetic Explosions.** One of the hazards of anesthesia is the occurrence of explosions, especially with ether, ethylene and cyclopropane, which form explosive mixtures with oxygen. The sources of ignition include static sparks, cauteries, open flames and motors and other electrical devices. Static sparks may be prevented by maintaining a high humidity or by the grounding of all apparatus used. The danger of explosion may be minimized by using the closed-circuit method of administration, in which the explosive gases are confined in the apparatus and not regularly released into the room air.

muscular relaxation for intra-abdominal operations. It is a satisfactory analgesic agent in obstetrics.

Vinyl ether was introduced in 1929 by Leake, who predicted that a chemical agent related to both ether and ethylene should possess desirable anesthetic properties. Its action is very rapid and the usual signs of deepening anesthesia may not be noted, so that precautions must be taken to avoid overanesthetization. It often produces troublesome salivation and may cause liver damage if administered for a long period or if hypoxia occurs during the procedure. It is used primarily for short surgical procedures, for the induction of anesthesia and during labor.

Trichloroethylene has recently been introduced as a general anesthetic, being more widely used in Great Britain than in the United States. It is apparently quite toxic and may cause cardiac arrhythmias. Its use is generally restricted to minor surgical procedures of short duration. It should not be administered by the closed method since it decomposes in the presence of soda lime, giving rise to toxic products.

Ethyl chloride is a potent general anesthetic agent. It produces a very rapid induction, and has been used principally for this purpose. Its toxicity resembles that of chloroform. It has largely been replaced as an induction agent by vinyl ether because of its toxicity. When sprayed upon the skin, it produces local anesthesia by cooling.

Chloroform is now generally considered to be too toxic for routine use, but its nonexplosibility and its relatively low volatility make it a useful agent where open flames cannot be avoided, and in hot climates, while the ease with which it can be administered is of value when hospital facilities are not available. It is a potent agent and can produce complete muscular relaxation in the presence of high concentrations of oxygen. Low concentrations of chloroform sensitize the heart muscle, as a consequence of which stimulation or the injection of epinephrine may result in acute ventricular

Ether produces a number of undesirable effects, including depression of liver function, irritation of the kidneys, elevation of blood sugar and acidosis. The so-called "ether convulsions" are probably not caused by ether, since they may occur during anesthesia with other agents. The cause of these convulsions is not definitely known. A number of factors are probably involved, including acute toxemia, hyperthermia, acidosis, hypoxia and carbon-dioxide retention.

Cyclopropane was introduced clinically by Waters in 1930, after preliminary studies by Lucas and Henderson had suggested its value as a general anesthetic. It produces a rapid and pleasant induction, and adequate muscular relaxation can be secured while high concentrations of oxygen are administered. Its chief disadvantages are its explosiveness and the occasional production of cardiac arrhythmias during deep anesthesia. The arrhythmias can usually be stopped by the addition of a small amount of ether vapor to the gas mixture. Bronchiolar spasm may be encountered during the administration of this agent. Because of its costliness, it is almost always administered by the closed, carbon-dioxide-absorption technic.

Nitrous oxide is the least toxic of the general anesthetics. Its disadvantage lies in the fact that deep anesthesia cannot be produced unless the oxygen concentration is reduced to a dangerously low level. Nitrous-oxide-oxygen anesthesia is almost always accompanied by some degree of hypoxia. As a supplement to other anesthetics, such as thiopental sodium or tribromoethanol, it is of considerable value. The use of nitrous-oxide-oxygen anesthesia for short dental procedures is very common but is not without hazards.

Ethylene was introduced as an anesthetic by Luckhardt and Carter in 1923. In spite of its unpleasant odor, it provides a rapid and pleasant induction and is comparatively nontoxic though its explosiveness in anesthetic mixtures is potentially dangerous. It is probably the anesthetic of choice for poor-risk patients but does not usually provide sufficient

administration may lead to its use by persons who are not qualified to recognize the danger signals of anesthesia.

Intravenous anesthesia is confined almost exclusively to the use of thiopental sodium (pentothal). Hexobarbital (evipal) is used to a certain extent, and recently two new ultra-short-acting barbiturates, kemithal and thioethamyl, have been introduced. Such agents as morphine, paraldehyde, alcohol and the longer-acting barbiturates have been used in the past but are considered unsafe.

Thiopental sodium, an ultra-short-acting barbiturate (see Chapter 7), was introduced clinically by Lundy in 1934. Its present popularity is due in no small measure to the experiences gained during its widespread use in World War II. It may be used alone, in combination with the weaker inhalation anesthetics, with regional anesthetics, or as a basal anesthetic in apprehensive patients. It is rapidly destroyed in the body and if administered slowly, fairly satisfactory "moment to moment control" can be attained. The mechanism of its detoxication has been in doubt, but recent evidence indicates that it, like the short-acting barbiturates, is destroyed in the liver. A moderate degree of liver damage does not constitute a contraindication to its use, since the duration of anesthesia is not prolonged. Laryngeal spasm may occur if the vocal cords are irritated by the presence of foreign material. The use of thiopental is therefore contraindicated in operations about the nose, mouth and throat, during which blood may run down and irritate the vocal cords. Oxygen should be administered during thiopental anesthesia because of the respiratory depression which the drug produces. The use of 50 per cent nitrous oxide and 50 per cent oxygen reduces the quantity of thiopental necessary for a surgical procedure, and at the same time provides the recommended increase of oxygen in the inspired atmosphere. Thiopental is contraindicated, or should be used with extreme caution in patients with recent severe hemorrhage or who are suffering from shock

fibrillation. High concentrations and rapid induction depress the heart to a dangerous degree and may lead to cardiac arrest. Resuscitation after chloroform overdosage is difficult since the circulation usually fails at the same time as respiration, whereas with other agents the heart generally continues to beat for some time after the cessation of respiration. A further disadvantage of chloroform is the frequent development of postanesthetic liver and kidney damage, especially in debilitated patients. There is some indication that this may be minimized by a high-carbohydrate diet or by the administration of choline or methionine.

Miscellaneous anesthetic agents whose clinical value has not been adequately determined include a series of compounds related to both ether and cyclopropane which have been prepared and studied by Krantz and his associates. These are ethyl cyclopropyl ether (cyprome ether), propyl cyclopropyl ether (cypreth ether) and its unsaturated analogue, known as cyprethylene ether. Other compounds studied by this group include isopropenyl vinyl ether (propethylene ether), an isomer of cyprethylene ether, and n-propyl methyl ether (metopryl), an isomer of ethyl ether.

**Combined Anesthesia.** Frequently, surgical anesthesia is effected by the use of several drugs and/or several methods so that the dose of each drug is minimal. An example of combined anesthesia would be adequate premedication, a regional block with procaine for analgesia and muscle relaxation, intravenous thiopental sodium for unconsciousness, nitrous-oxide-oxygen for analgesia and unconsciousness, and the provision of increased oxygen supply for the patient during the operative procedure.

### INTRAVENOUS ANESTHESIA

Intravenous anesthesia offers the advantages of rapid induction, simplicity of administration and absence of explosion hazards. Its disadvantages include all those inherent in intravenous therapy while the very simplicity of its

Although curare was used clinically in 1859 in an attempt to control tetanus convulsions, its use was abandoned because of the uncertain supply and the variable potency of the drug. In 1938, however, intocostin, a purified and standardized preparation, became available and was used successfully to secure skeletal-muscle relaxation during the shock therapy of mental disorders. It was first used to secure muscular relaxation in anesthesia by Griffith and Johnson in 1942 and in the following years its use became widespread. It must be remembered that curare is not an anesthetic agent in itself and is used only as an adjunct to anesthesia.

Curare preparations currently in clinical use include intocostin, 20 units per cc., and d-tubocurarine chloride, 3 mg./cc. The activity of 20 units of intocostin is equivalent to that of 3 mg. of d-tubocurarine. The latter is apparently the active principle of curare. It was first isolated by King in 1935 and its structural formula has been tentatively identified.

Curare is a useful adjunct to such anesthetics as thiopental, nitrous oxide and cyclopropane since it induces satisfactory muscular relaxation without the use of dangerously high concentrations of anesthetic. The usual procedure is to administer intravenously from 40 to 100 units of intocostin or from 6 to 15 mg. of d-tubocurarine chloride when the patient is in light surgical anesthesia. Muscular relaxation usually occurs in about 2 minutes. The effects persist for from 15 to 30 minutes or longer; additional injections may be given as required. The dosage should be reduced by at least one-third if used with ether since this agent has a curare-like action in itself. Curare preparations abolish many of the conventional signs for estimating the depth of anesthesia and unless adequate precautions are taken either over- or under-anesthetization may occur. Overdosage with curare results in paralysis of the respiratory muscle, hence facilities for artificial respiration with

or toxemia, since the tolerance to thiopental is greatly reduced in these conditions. It should be administered in concentrations of 2.5 per cent or less, since the use of more concentrated solutions may cause venous thrombosis.

### RECTAL ANESTHESIA

The administration of anesthetics by rectum is seldom resorted to at the present time, since the method is cumbersome and the variations in the rate of absorption make the end results unpredictable. The first preparation to receive considerable use was Gwathmey's oil-ether mixture, a solution of ether in olive oil. This mixture was later modified for obstetric anesthesia by the addition of magnesium sulfate, which was thought to act synergistically with the ether. Even in such mixtures, however, the ether may be irritating to the rectal mucosa.

More recently a solution of tribromoethanol in amylene hydrate (avertin, bromethol) has been used. When first introduced it was used to produce general anesthesia. The narrow margin of safety between anesthetic and toxic doses led to abandonment of its use for this purpose, and it is now employed largely as a basal anesthetic, especially in children. Its chief toxic effect lies in its profound depressant action on the respiratory center. The shorter-acting barbiturates, such as pentobarbital, amytal and thiopental, are also used rectally as basal anesthetics. Paraldehyde has been administered by this route to produce obstetric analgesia but it is too unreliable to be acceptable.

### CURARE

Curare is a crude drug of indefinite composition obtained from a number of South American plants. Its predominant pharmacologic action is paralysis of voluntary muscle, an action shown by Claude Bernard in 1844 to originate at the neuromuscular junction. It has long been known and used by the natives of South America as an arrow poison.

of anoxemia which may develop during the administration of general anesthetics. While the term anoxia is generally used, the term hypoxia is more accurate since the lack of oxygen is relative, not absolute.

The following four classes of anoxia are generally recognized:

1. Anoxic anoxia (anoxemia), due to a low oxygen tension in the alveolar air and the blood, with a resultant reduction in the saturation of the hemoglobin with oxygen. This may arise during anesthesia, at high altitudes, during pulmonary infections, from shallow respirations or from congenital malformations of the heart and blood vessels.
2. Anemic anoxia, in which the blood oxygen tension is normal but there is a deficiency of functioning hemoglobin. This may occur with the anemias, hemorrhage or with agents which interfere with oxygen transport by hemoglobin, such as carbon monoxide, chlorates, nitrites and coal-tar derivatives.
3. Stagnant anoxia, in which the tissues receive insufficient oxygen because of a slowing of the circulation as in shock and conditions of impaired venous return.
4. Histotoxic anoxia, in which the tissue cells are poisoned and cannot utilize oxygen, as in poisoning by cyanides and other cellular depressants.

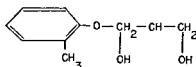
Symptoms of anoxia include dyspnea followed by slow, labored breathing and coughing; tachycardia or, later, a slow bounding pulse and an increased blood pressure followed by a terminal fall; gastro-intestinal disturbances including abdominal cramps, nausea and vomiting and diarrhea; and cerebral changes manifested by irritability, restlessness, headache, confusion and delirium. The presence of cyanosis is a useful though not altogether reliable index of oxygen want since it depends on the amount of reduced hemoglobin in the peripheral capillaries and on the degree of vascular dilation or constriction. Five grams of reduced hemoglobin per 100 cc. blood are necessary for



oxygen should always be available when curare preparations are used. Neostigmine is a pharmacologic antidote to curare and may be administered if signs of respiratory embarrassment appear. The undesirable parasympathomimetic effects of neostigmine can be controlled with atropine. Neostigmine is rarely necessary, however, since the treatment of choice is artificial respiration with oxygen until adequate respiratory activity returns.

Myasthenia gravis patients are particularly sensitive to curare; the drug has been used as a diagnostic aid when this condition is suspected. It should be used in minute amounts, however, lest respiratory paralysis occur. It has also been used to relieve spastic states and to facilitate bronchoscopy and tracheal intubation.

Recently, a synthetic preparation with a curare-like effect has received preliminary clinical trials in Great Britain. This compound,  $\alpha$ ,  $\beta$ , dihydroxy, (2 methyl) phenoxypropane, known as myanesin or B.D.H. 312, appears to exert



its muscular-relaxing action by a depressant action on the reflex excitability of the spinal cord. It appears to be much less toxic than curare, and intercostal paralysis does not occur with doses producing full abdominal relaxation.

Erythroidine, an alkaloid with a curare-like action, is present in various species of erythrina. Although a satisfactory substitute for curare, it appears to have had little clinical use. Its action is less prolonged than that of curare.

### OXYGEN THERAPY

Oxygen alone, or mixtures of oxygen with carbon dioxide or an inert gas such as helium are of great value in the treatment of various types of anoxia or hypoxia, including

the anoxemia which may develop during the administration of general anesthetics. While the term anoxia is generally used, the term hypoxia is more accurate since the lack of oxygen is relative, not absolute.

The following four classes of anoxia are generally recognized:

1. Anoxic anoxia (anoxemia), due to a low oxygen tension in the alveolar air and the blood, with a resultant reduction in the saturation of the hemoglobin with oxygen. This may arise during anesthesia, at high altitudes, during pulmonary infections, from shallow respirations or from congenital malformations of the heart and blood vessels.
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Symptoms of anoxia include dyspnea followed by slow, labored breathing and coughing; tachycardia or, later, a slow bounding pulse and an increased blood pressure followed by a terminal fall; gastro-intestinal disturbances including abdominal cramps, nausea and vomiting and diarrhea; and cerebral changes manifested by irritability, restlessness, headache, confusion and delirium. The presence of cyanosis is a useful though not altogether reliable index of oxygen want since it depends on the amount of reduced hemoglobin in the peripheral capillaries and on the degree of vascular dilation or constriction. Five grams of reduced hemoglobin per 100 cc. blood are necessary for

cyanosis to be apparent. A patient with severe anemia may die of oxygen want but never be cyanotic.

Indications for oxygen therapy include operations on anemic and toxic patients; any condition interfering with pulmonary function; poisoning by depressant drugs, such as morphine, barbiturates and general anesthetics; severe toxemias; coronary thrombosis and decompensated heart disease and surgical and traumatic shock.

Oxygen may be administered by means of a face mask, by nasal catheter or by placing the patient in an oxygen tent or specially constructed oxygen chamber. If given by the catheter technic, the oxygen should be humidified; otherwise it will irritate the respiratory passages. If administered in a closed circulation, provisions must be made for removal of the carbon dioxide. If an oxygen tent is used, provision must be made to cool the tent atmosphere, and the oxygen concentration in the tent should be determined frequently. Oxygen must not be administered in the presence of open flames, cautery or electric motors because of the fire hazard.

### PREPARATIONS

Ether U.S.P. Anesthetic ether B.P.

Cyclopropane U.S.P.; B.P.

Nitrous oxide U.S.P.; B.P.

Ethylene U.S.P.; B.P.

Vinyl ether U.S.P.

Trichloroethylene U.S.P.

Ethyl chloride U.S.P.; B.P.

Chloroform U.S.P.; B.P.

Thiopental sodium U.S.P. Soluble thiopentone B.P.

Hexobarbital soluble N.N.R. Hexobarbitone B.P.

Tribromoethanol U.S.P.; B.P.

Tribromoethanol solution U.S.P.; B.P. A solution of tribromoethanol in amylene hydrate containing 100 Gm. of tribromoethanol in 100 cc.

Oxygen U.S.P.; B.P.  
Intocostin N.R.  
D-tubocurarine chloride N.R.

## BIBLIOGRAPHY

## GENERAL

Adriani, J.: The Pharmacology of Anesthetic Drugs, Springfield, Ill., Thomas, 1942.  
Adriani, J.: The Chemistry of Anesthesia, Springfield, Ill., Thomas, 1946.  
Keys, T. E.: The History of Surgical Anesthesia, New York, Schuman, 1945.  
Mourel, L. H., D. Stubbs and J. Kreiselman: Anesthetic complications and their management, Anesthesiology 7: 69, 1946.  
Weiss, W. A., and L. H. Mourel: Preoperative and post-operative sedation, Surg. Clin. North America 25: 1057, 1945.

## INHALATION ANESTHESIA

Clement, F. W.: Nitrous Oxide-Oxygen Anesthesia—McKessen-Clement Viewpoint and Technique, Philadelphia, Lea, 1945.  
Cole, F.: Explosions in anesthesia—a review of the literature, Surgery 18: 7, 1945.  
Guedel, A. E.: Inhalation Anesthesia, New York, Macmillan, 1937.  
Livingstone, H. M.: The present status of ethylene-oxygen anesthesia, Ann. Surg. 122: 1071, 1945.  
Waters, R. M.: Cyclopropane—a personal evaluation, Surgery 18: 26, 1945.

## INTRAVENOUS ANESTHESIA

Adams, R. C.: Intravenous Anesthesia, New York, Hoeber, 1944.  
Adams, R. C.: Principles of intravenous anesthesia with pentothal sodium, Surg. Clin. North America 25: 788, 1945.

## CURARE

Berger, F. N., and W. Bradley: Muscle-relaxing action of myanesin, Lancet 1: 97, 1947.

- Berger, F. N., and W. Bradley: The pharmacological properties of d:B di-hydroxyl- $\gamma$ -(2 methyl-phenoxy)-propane (myanesin), *Brit. J. Pharmacol.* 1:265, 1946.
- Cullen, S. C.: Curare in anesthesia, *Surgery* 18:45, 1945.
- Gray, T. C., and J. Halton: A milestone in anesthesia (d-tubocurarine chloride), *Proc. Roy. Soc. Med.* 39:400, 1946.
- McIntyre, A. R.: Curare, Its History, Nature and Clinical Use, Chicago, Chicago Univ. Press, 1947.

#### OXYGEN THERAPY

- Andrews, A. H., Jr.: Manual of Oxygen Therapy Techniques, Chicago, Yr. Bk. Pub., 1943.
- Barach, A. L.: Principles and Practices of Inhalational Therapy, Philadelphia, Lippincott, 1944.

# Regional Anesthesia

6

INTRODUCTION  
REGIONAL ANESTHETIC AGENTS  
REFRIGERATION ANESTHESIA  
PREPARATIONS  
TOPICAL ANESTHESIA  
INJECTION ANESTHESIA

## INTRODUCTION

Regional (local) anesthesia consists of loss of pain in a circumscribed area of the body without loss of consciousness. It may be produced by the application of cold, pressure on the nerve trunks or by tissue anæmia; by such agents as phenol or quinine; or by drugs which depress sensory nerves such as cocaine and its various synthetic substitutes, either applied locally to mucous surfaces or injected by means of a hypodermic syringe (Table 2).

Table 2  
LOCAL ANESTHETIC AGENTS GROUPED ACCORDING TO THEIR CLINICAL USE

AGENTS SUITABLE FOR TOPICAL ANESTHESIA ONLY	AGENTS SUITABLE FOR INJECTION ANESTHESIA ONLY	AGENTS SUITABLE FOR TOPICAL AND INJECTION ANESTHESIA
Cocaine Tutocaine (also subcutaneous) Phenacaine Ethylaminobenzoate Butacaine Diothane Amylaine Butylaminobenzoate Butesin picrate Orthoform	Procaine Apothesine Larocaine	Tetracaine Amydracaine (too toxic for spinal) Metycaine Dibucaine

## TOPICAL ANESTHESIA

No local anesthetic agent is absorbed in effective concentrations through the skin, with the exception of phenol, which is now considered too toxic to be used clinically. Cocaine and some of its synthetic substitutes, such as phenacaine, tetracaine and butacaine, are absorbed through mucous membranes and are of value in eye, nose and throat work or in urology. Some preparations as butyl aminobenzoate, butesin picrate, ethyl aminobenzoate and orthoform are highly insoluble and may be applied to open wounds or burns since they penetrate the tissues very slowly. Cocaine should never be used in conditions permitting rapid absorption because of its high systemic toxicity.

## INJECTION ANESTHESIA

Procaine and related compounds are the most widely used agents for injection anesthesia. Alcohol and quinine salts find limited use because of their irritating properties, although they possess the advantage of a prolonged anesthetic action which may be useful in the relief of neuralgic pain.

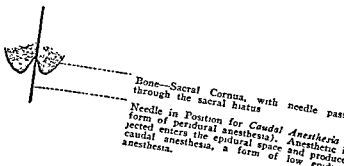
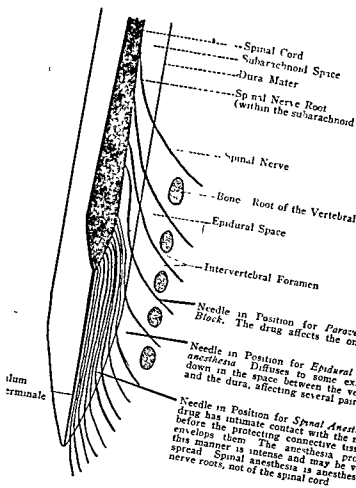
Injection anesthesia may be effected by local infiltration, field block or nerve block. In *infiltration* anesthesia, the anesthetic agent is injected intracutaneously and subcutaneously at the desired site of incision or in a painful area. In *field block*, injections are made around the site of incision, cutting off the nerve supply to the area without rendering it edematous as in local infiltration. In *nerve-block technics*, the nerve supplying the field of operation is blocked by the accurate placement of the anesthetic agent in or around the nerve trunk at some distance from the operative field. Special forms of nerve block include *peridural* anesthesia, in which the spinal nerves are blocked by agents placed in the peridural space, and *spinal* or *intradural* anesthesia, in which the agents are placed in the subarachnoid space. The former results in a slower onset

of anesthesia since the agent must penetrate the perineural sheath before reaching the nerve trunk. Since the spread of the anesthetic drug is more limited than with spinal, there is less danger of producing respiratory depression or paralysis. With intradural anesthesia, the onset is rapid, the reaction more intense but upward diffusion of the drug through the cerebrospinal fluid may lead to respiratory depression and failure because of paralysis of the intercostal and phrenic nerves.

Spinal anesthesia may be used for all operations below the diaphragm. If the drug is permitted to ascend to a higher level, respiratory paralysis may occur. It offers the advantages of maximal muscular relaxation and little or no postoperative vomiting. It should not be used in nervous or apprehensive patients, in children or in very old patients, in the presence of degenerative heart diseases or of, very high or low blood pressure, in patients with deformities of the spine, in the presence of infections in the region of injection, and in patients with diseases of the central nervous system.

The choice injection site in spinal anesthesia is the third or fourth lumbar interspace. The height to which anesthesia ascends depends upon the amount of anesthetic injected, the force with which it is injected, the specific gravity of the injected fluid and the position of the patient. The specific gravity of normal spinal fluid is about 1.007. Solutions for spinal anesthesia which have a higher specific gravity than 1.007 are called hyperbaric; those with lower specific gravity are called hypobaric; if the specific gravity of the solution is equal to that of the spinal fluid, it is called isobaric. After injection into the spinal canal, isobaric solutions do not tend to shift position. If the patient is not horizontal, however, hyperbaric solutions run downward and hypobaric solutions float upward in the spinal fluid. Caudal anesthesia is a special type of peridural anesthesia in which the anesthetic agent is introduced through





the sacral hiatus into the caudal canal. It is used in obstetrics and for surgery of the perineal region. Both caudal and spinal anesthesia can be administered either by single or by repeated doses. For the latter purpose, a special needle or catheter is generally left in place and fresh solution injected as conditions demand, i.e., the so-called continuous spinal or caudal anesthesia.

Saddle-block anesthesia is a special type of spinal anesthesia in which the effect of the drug is limited to the lowest spinal nerves and anesthesia is produced in the perineal area. It has the advantage of producing minimal changes in the cardiovascular system and of having no effect on respiration and on uterine contractions.

## REGIONAL ANESTHETIC AGENTS

The ideal drug for regional anesthesia should be stable, water-soluble, nonirritating to tissues or nerves and of low systemic toxicity. It should provide an adequately long period of anesthesia with a prompt onset, and on recovery (paresthesias) should not be present. Finally, it should be capable of withstanding sterilization and should be relatively inexpensive.

The injection of a regional anesthetic agent does not result in an immediate paralysis of all nerve fibers. The autonomic fibers are affected first, then the sensory, and finally the motor. According to Gasser and Erlanger, the size of the constituent fibers is the most important factor, the smallest fibers being the most susceptible. Pain is the first sensation to disappear, followed by cold, warmth, touch, joint and deep pressure. Recovery results in the return of sensations in the reverse order.

Potentiation of Local Anesthetics. The addition of a vasoconstrictor such as epinephrine to local anesthetic agents results in an increased duration of anesthesia and a lowered threshold concentration since absorption of the

drug is retarded by the vasoconstriction. Epinephrine is most commonly used for this purpose (see Chapter 11).

The addition of alkali to local anesthetic agents increases their efficiency to the extent that the free bases penetrate tissues more readily than their salts. However, the use of the free base would only be of advantage in topical anesthesia. The free bases, although more potent, are so insoluble as to be impractical for injection anesthesia, and the local anesthetics are generally marketed as the hydrochloride salt. Since their activity is due to the liberation of free base by the tissue fluids, it is difficult to obtain a proper degree of anesthesia in an acutely inflamed area or wherever an acid reaction in the tissues is encountered.

**Biologic Assay.** Various technics are used for testing local anesthetic agents. Cocaine or procaine usually serves as the standard of reference. Topical anesthesia can be assayed by the duration of loss of sensation occasioned by placing the agent on the mucosa of the human tongue, in the rabbit's cornea or on the frog's skin. Infiltration anesthesia may be

TABLE 3  
COMPARATIVE TOXICITY OF  
VARIOUS LOCAL ANESTHETIC AGENTS

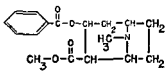
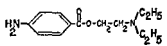
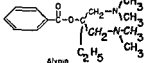
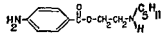
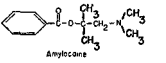
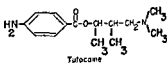
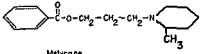
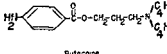
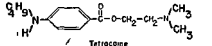
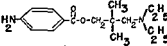
DRUG	SUBCUTANEOUS LD <sub>50</sub> FOR GUINEA PIGS IN MG./KG. (TOTAL SAFE DOSE FOR HUMANS)
Procaine (novocaine) .....	430
Eucaine (Beta-eucaine) .....	310
Metycaine (neothessin) .....	300
Larocaine .....	200
Amylocaine (stovaine) .....	200
Tutocaine .....	190
Butacaine .....	70
Amydricaine (alypin) .....	70
Cocaine .....	50
Phenacaine (holocaine) .....	50
Tetracaine (pontocaine) .....	30
Dibucaine (nupercaine, percaïne) .....	10

tested by raising an intradermal wheal in human beings or guinea pigs. Rabbits are usually used for the study of spinal anesthesia. Toxicity is generally determined by injecting the agent subcutaneously into laboratory animals. Bieler has shown that the subcutaneous  $LD_{50}$  for guinea pigs, expressed as mg./Kg., is equivalent to the total safe dose in mg. for human beings; values for the more commonly used agents are presented in Table 3. The  $LD_{50}$  may be greatly increased by prior administration of barbiturates.

**Toxicity.** Toxic reactions from local anesthetic agents may result from idiosyncrasy, from rapid absorption from the site of injection, or from accidental intravenous injection. Symptoms include excitement, apprehension and anxiety, dizziness, severe headaches, convulsions and fall in blood pressure. Death is due to cardiovascular collapse and respiratory failure. Prophylactic measures include slow injection, the use of dilute solutions, aspiration to insure that intravascular penetration has not occurred, the addition of epinephrine or other suitable vasoconstrictors to decrease the rate of absorption, and the administration of pressor drugs, such as ephedrine, to combat the fall of pressure which occurs in spinal anesthesia following paralysis of the sympathetic nerves. The administration of a short-acting barbiturate an hour or so before anesthetization does much to reduce the central stimulation.

Treatment of acute symptoms of poisoning include immediate interruption of administration, intravenous barbiturates to control convulsions, injections of epinephrine to combat the fall in blood pressure, and the use of oxygen and artificial respiration to combat respiratory depression. In spinal anesthesia, withdrawal of a small volume of spinal fluid may result in the removal of appreciable quantities of the drug. If the injection was made in an extremity, a tourniquet should be applied proximal to the injection site, in order to stop further absorption of the drug.

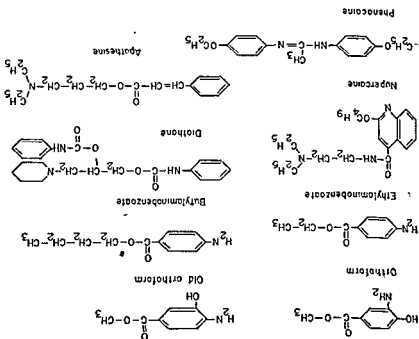
**Metabolism.** Local anesthetic agents are hydrolyzed chiefly by the liver; the variations in their toxicity are proportional to the rate at which they are metabolized. One of the products of hydrolysis of procaine and related compounds is para-aminobenzoic acid, which may interfere

 <p>Cocaine</p>	 <p>Procaine</p>
 <p>Atypha</p>	 <p>Amylne</p>
 <p>Amylocaine</p>	 <p>Tufocaine</p>
 <p>Metycane</p>	 <p>Butacaine</p>
 <p>Tetrocaine</p>	 <p>Larcocaine</p>

with the activity of concomitantly administered sulfonamides (see Chapter 29).

**Chemistry.** Because of the toxicity of cocaine and its tendency to produce habituation, numerous compounds have been synthesized in the hope of developing a less dangerous analogue. The structures of the more important of these and their relation to cocaine are shown above. Other

of active local anesthetic agents are shown on this page. The lack of specificity for local anesthetic action is well illustrated by the diverse nature of the synthetic compounds, although it can be seen that the most widely developed class is that of the alkamine esters of benzoic or para-amino-benzoic acid. Alterations in the length of the alkyl chain or in the nature of the substitutions on the amino group result in only minor changes in pharmacologic action.



Cocaine is an alkaloid obtained from the leaves of *Erythroxylon coca*, a tree indigenous to Peru, Chile and Bolivia. For centuries, the Indians of South America have chewed coca leaves mixed with an alkali, such as lime or charcoal, to allay hunger and to increase endurance. The alkaloid was first isolated by Gaedecke in 1855 and became known as erythroxylin. It was rediscovered in 1859 by Niemann, who named it cocaine. Its anesthetic properties were first noted by Wohler in 1860, but it was not

introduced clinically until 1884, when Koller demonstrated its usefulness as a topical anesthetic in ophthalmology. In 1885, Halsted used cocaine for nerve-block anesthesia and in the same year Corning used it experimentally as a spinal anesthetic in dogs. It was introduced for this purpose in patients by Bier in 1898 and its adoption immediately became widespread until its toxicity was realized, whereupon it soon was replaced by less toxic substitutes.

The use of cocaine is now limited to surface application. It should not be used where repeated administration is necessary, since this may lead to habit formation, which is characterized by alternate periods of elation and depression, loss of appetite and weight, insomnia and moral degeneration. Sensory hallucinations are common. Cocaine is frequently taken by addicts as a snuff, which may lead to nasal abscesses.

The acute toxic effects of cocaine are those of central stimulation, followed by depression, and stimulation of the sympathetic nervous system. The latter effect is apparently due to a suppressive action on the amine oxidase (see Chapter 11) and is manifested by such effects as pupillary dilation, vasoconstriction and tachycardia. Cocaine has a pyretic action, possibly due to a direct action on the temperature-regulating center.

Procaine (novocaine) was prepared by Einhorn in Germany in 1905. It is much less toxic and almost as effective by injection as cocaine, although it is not so rapidly absorbed from mucous surfaces. It is probably the most widely used agent for injection anesthesia. It does not possess the habit-forming properties or the sympathomimetic action of cocaine.

Procaine is detoxified rapidly by the liver and may be administered intravenously if injections are given slowly and high dilutions of the drug are used. Intravenous procaine has recently been used in the treatment of painful burns and injuries and in childbirth. It apparently affects the

nerve endings in the painful region in concentrations too low to affect those in other parts of the body. Intravenous procaine has also been used in the treatment of serum sickness and to protect the heart in cyclopropane anesthesia. Muscle aches and sprains may often be dramatically and permanently relieved by the local infiltration of procaine. Procaine is used for infiltration anesthesia in concentrations of 0.25 to 1.0 per cent combined with epinephrine (1:100,000 to 1:200,000). Approximately from 2 to 4 cc. of a 5 per cent solution are usually used for spinal anesthesia.

Dibucaine (nupercaine) is a quinine derivative prepared by Uhlmann in 1929. It combines the qualities of cocaine and procaine in that it is effective both for topical and injection anesthesia. It is more toxic than cocaine but its anesthetic properties are correspondingly greater. It is used in concentrations of from 1 in 2,000 to 1 in 1,000 for infiltration anesthesia, and in 1 in 1,500 solution for spinal anesthesia, the average dose being from 10 to 15 cc.

Metycaine was first prepared by McElvain in 1927. Like dibucaine, it is effective both topically and by injection. It is somewhat more toxic than procaine. It is applied to mucous surfaces in concentrations of from 2 to 10 per cent and is used in 0.5 to 1 per cent solutions in infiltration anesthesia. It has also been used as a spinal anesthetic. Tetracaine (pontocaine) has recently been used quite extensively for spinal and caudal anesthesia. It is much more toxic than procaine, but gives a prolonged period of anesthesia. Spinal anesthesia may be achieved with from 2 to 4 cc. of a 0.5 per cent solution.

Eucaine (Beta-eucaine) and amylocaine (stovaine) are mainly of historical interest. Eucaine was one of the earliest cocaine substitutes being synthesized by Vinci in 1897. It is somewhat less toxic than cocaine but is fairly irritating to the tissues. It is no longer included in the United States Pharmacopoeia. Amylocaine was synthesized by Fournneau



in 1904 and still finds some use, particularly in Europe, as a spinal anesthetic. It is irritating, however, and highly toxic.

### REFRIGERATION ANESTHESIA

Refrigeration anesthesia was introduced by Allen in 1941. It is applicable only to the extremities. Surgery may be effected with a minimum of shock and blood loss. It is of particular value for amputations of severely traumatized or gangrenous limbs. Absorption of toxic products is prevented by the application of a tourniquet, and pain is alleviated by a rapid cooling of the limb to from 2° to 8° C. by application of ice or by a refrigeration machine. At this temperature, the activity of the tissues is suspended and the spread of infections halted; hence, amputation can be delayed for several days if necessary. Refrigeration without tourniquet has on occasion saved a badly infected limb that would otherwise have had to be amputated.

### PREPARATIONS

Cocaine U.S.P.; B.P.

Cocaine hydrochloride U.S.P.; B.P.

Procaine hydrochloride U.S.P.; B.P. Procaine borate N.N.R.

Procaine nitrate N.N.R.

Tetracaine hydrochloride U.S.P. Amethocaine hydrochloride B.P.

Phenacaine hydrochloride U.S.P.

Ethyl aminobenzoate U.S.P. Benzocaine B.P.

Ethyl aminobenzoate ointment U.S.P.; 5 per cent ethyl aminobenzoate in white ointment.

Butacaine sulfate U.S.P.

Butyl aminobenzoate U.S.P.

Amylocaine hydrochloride B.P.

Amydracaine hydrochloride N.N.R.

Amylsine hydrochloride N.N.R.

Apothesin  hydrochloride N.N.R.

Diothane hydrochloride N.N.R.

Allen, F. M.: Intravenous obstetric anesthesia—preliminary report, *Am. J. Surg.* 70:283, 1945.

Brown, H. O., J. M. Thomson and J. E. Fitzgerald: An analysis of 500 obstetrical cases with continuous caudal anesthesia using pontocaine, *Anesthesiology* 7:355, 1946.

Burn, J. H.: The testing of local anaesthetics, *Brit. M. Bull.* 4:82, 1946.

Fraser, R. J.: Continuous spinal or lumbar anaesthesia, *Canad. M. A. J.* 54:363, 1946.

Gasser, H. S., and J. Erlanger: The rôle of fiber size in the establishment of a nerve block by pressure or cocaine, *Am. J. Physiol.* 88:581, 1929.

Gordon, R. A.: Intravenous novocaine for analgesia in burns, *Canad. M. A. J.* 49:478, 1943.

Hershey, S. G.: Imperfections of spinal anesthesia, *New York State J. Med.* 45:1761, 1945.

Hirschfelder, A. D., and R. N. Bieter: Local anesthetics, *Physiol. Rev.* 12:190, 1932.

Johnson, K., and C. R. A. Gilbert: Intravenous procaine for obstetrical anesthesia, *Anesth. & Analg.* 25:133, 1946.

Knoetel, P. K., R. P. Herwick and A. S. Loevenhart: The prevention of acute intoxication from local anesthetics, *J. Pharmacol. & Exper. Therap.* 39:397, 1930.

Lull, C. B., and R. A. Hingson: Control of Pain in Child-birth, Philadelphia, Lippincott, 1945.

Maxson, L. H.: Spinal Anesthesia, Philadelphia, Lippincott, 1938.

# GENERAL

## BIBLIOGRAPHY

Larocaine hydrochloride N.N.R.  
 Metycaine hydrochloride N.N.R.  
 Dibucaine hydrochloride N.N.R.  
 Tutocaine hydrochloride N.N.R.  
 Monocaine hydrochloride N.N.R.  
 Butesin picrate N.N.R.  
 Orthoform N.N.R.

Pitkin, G. P.: *Conduction Anesthesia*, Philadelphia, Lippincott, 1946.

State, D., and O. H. Wangenstein: Procaine intravenously in treatment of delayed serum sickness, *J.A.M.A.* 130:990, 1946.

#### REFRIGERATION ANESTHESIA

Allen, F. M.: Reduced temperatures in surgery—I. Surgery of limbs, *Am. J. Surg.* 52:225, 1941.

Crossman, L. W., and F. M. Allen: Shock and refrigeration, *J.A.M.A.* 130:185, 1946.

Kanaar, A. G.: Refrigeration in the treatment of trauma, with review of cryotherapy, *Anest. & Analg.* 25:177, 228, 1945.

Melick, D. W.: *Refrigeration anesthesia*, *Am. J. Surg.* 70:364, 1945.

# Hypnotics and Sedatives

7

INTRODUCTION	SULFONAL
BARBITURATES	BROMIDES
CHLORAL HYDRATE	ANTIEPILEPTIC DRUGS
PARALDEHYDE	

## INTRODUCTION

Hypnotics are drugs used to induce sleep when sleeplessness is not due to a definite stimulus, such as pain, dyspnea or itching, which prevents sleep or awakens the patient. Sedatives are drugs which allay excitement and reduce motor activity without necessarily inducing sleep. Hypnotics in small doses usually have a sedative action.

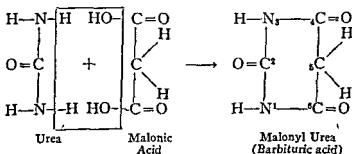
The choice of hypnotics depends to a large extent on the nature of the insomnia. The patient may have difficulty in falling asleep but once asleep may rest soundly. In such cases a drug acting promptly but with a short duration of action will suffice. A longer-acting drug is indicated for patients who fall asleep readily but awaken during the night and fall asleep again with difficulty or for patients who experience periods of wakefulness during the night. Such types of insomnia are usually due to some emotional disturbance and wherever possible the underlying cause should be treated without recourse to drugs. Hypnotics should be prescribed only if the emotional tension is transitory, such as anxiety preceding a surgical operation or grief at a bereavement, or if the lack of sleep is seriously impairing the patient's health and welfare.

Hypnotics, with the exception of morphine, do not relieve pain though they may dull the consciousness of pain perception sufficiently to permit sleep. Ideally, a hypnotic should have no subsidiary effects on the circulation, respiration or metabolism. It should cause no pre-excitement or post-depression and should rapidly produce a natural sleep from which the patient awakes refreshed and relaxed. The efficacy of a hypnotic is enhanced if, in addition, sleep-inducing conditions such as a quiet and darkened room, adequate warmth and the absence of exciting stimuli are provided.

### BARBITURATES

Barbituric-acid derivatives were introduced into medicine in 1903 when the hypnotic action of diethyl barbituric acid (barbital, veronal) was established by Fischer and von Mering. Since that time, hundreds of derivatives have been studied, partly because of the ease with which such compounds can be prepared and tested and partly because of the great demand for barbiturates not only as hypnotics but also as sedatives, anticonvulsants, basal anesthetics and general anesthetics.

**Chemistry.** Barbituric acid (malonyl urea) is prepared by the condensation of urea with malonic acid:



The replacement of both hydrogen atoms in position 5 by alkyl or aryl groups results in compounds with a hypnotic action. If the substituting groups are chemically stable, the

compounds appear to be stable under the metabolic conditions of the body and are long-acting. If the groups contain branched chains or double bonds, they are apt to be more rapidly destroyed in the body and thus are short-acting. Replacement of the oxygen in the 2 position by sulfur results in compounds known as thiobarbiturates which have exceptionally short periods of action. Thiopental sodium (pentothal) is an example of this group. Substitution in the 1 and 3 positions may result in compounds having a convulsant action.

The substituted barbituric acids are not very soluble in water but are fairly stable. The sodium salts are readily soluble in water but the solutions are not very stable and may form toxic decomposition products. When barbiturates are used intravenously, fresh solution of the sodium salts should be prepared.

Pharmacology. Therapeutic doses of barbiturates have little action other than depression of the higher brain centers. In toxic doses they also depress the spinal cord. At higher dosage levels they may have a mildly depressant action on smooth muscle and on the kidney. The heart is not affected by therapeutic doses, but may be secondarily affected by toxic doses which cause profound respiratory depression and peripheral vasodilatation.

In vitro, the barbiturates have a depressant effect on the carbohydrate metabolism of the brain, probably through an interference with oxidation-reduction reactions of flavoprotein by the cytochrome system. Since the oxidation of succinate is not affected, antagonism of barbiturate-induced depression by large doses of succinate is theoretically possible. In practice, the metabolism of succinate by the liver is so rapid that usually inadequate amounts are available to the brain, and the administration of succinate to barbiturate-poisoned animals or man has for the most part yielded erratic results.

**Classification.** Barbiturates can be conveniently classified according to duration of hypnotic action. Barbiturates with a *long* action include phenobarbital (luminal) and barbital (veronal); with an *intermediate* action, amytal, dial, probarbital (ipral), alurate and neonal; with a *short* action, nostal, ortal, pentobarbital (nembutal), phanodorn, pernoston, seconal, sandoptal and vinbarbital; and with an *ultra-short* action, effective only when given intravenously, hexobarbital (evipal) and thiopental sodium (pentothal).

**Clinical Uses.** The most common use of barbiturates is for the treatment of insomnia. Their use as basal and general anesthetics is discussed in Chapter 5. They are effective antidotes for convulsant poisons, pentobarbital and amytal being probably the most useful drugs for this purpose. Amytal has found special use in psychiatry to produce a state comparable to hypnosis (amytal interview) in which the patient will talk freely and be susceptible to suggestions. The use of phenobarbital in the treatment of epilepsy is discussed under antiepileptic drugs in this chapter.

**Toxicity and Antidotes.** Acute barbiturate poisoning, either from accidental overdosage or from suicidal attempts is one of the most common forms of drug toxicity encountered in present-day practice. The symptoms are nonspecific. Usually there is confusion, ataxia, vomiting, motor excitement followed by coma, shallow, rapid respiration, fixed miotic pupils, thready pulse, low blood pressure and absence of reflexes. The specific antidote for barbiturate poisoning is picrotoxin. It should be given in small repeated doses or by continuous infusion at the rate of approximately 1 mg. per minute until the wink reflex returns. The dosage can then be reduced but the drug should not be discontinued until consciousness returns since it is rapidly detoxified by the body, following which severe depression may again set in. Supportive measures include gastric lavage and intravenous fluids to promote diuresis and thus assist in the removal of the drug. Artificial respiration may be necessary if the respiration is greatly depressed.

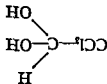
Amphetamine sulfate, by intravenous injection, has also been used in the treatment of acute barbiturate poisoning. It is less liable to cause convulsions than is picrotoxin and is usually more readily available.

A particular danger of barbiturates is that a single dose may lead to a mental dulling and a disorientation as to time and place; consequently, the patient may take additional doses, and accidental intoxication may ensue. Repeated use of barbiturates may lead to habituation; a marked craving for the drug may be developed but true abstinence symptoms do not follow its withdrawal. It is debatable whether prolonged use of the barbiturates leads to chronic poisoning though there is considerable evidence to indicate that this is the case. Degenerative changes have been reported in animals given barbiturates over long periods and clinical reports suggest that mental deterioration may occur in man after long-continued administration.

Occasionally individuals are hypersensitive to barbiturates or may display side-actions or excitement and delirium after therapeutic doses. Dermatologic lesions are not infrequent and are manifested as wheals or an angioneurotic edema or by skin rashes which resemble measles or scarlet fever. These lesions occur more frequently with long-acting than with short-acting barbiturates.

The dangers of promiscuous use of barbiturates has led to their being available only on a physician's prescription in many states. As a further precaution, it is advisable to limit the amount prescribed to a minimum and to designate the prescriptions are nonrefillable.

## CHLORAL HYDRATE





Chloral hydrate was introduced into medicine by Liebreich in 1869. It achieved immediate popularity as a hypnotic, morphine being the only other such drug available at that time. It still remains one of the safest, best and least expensive hypnotics. It acts rapidly because of its ready solubility and produces a natural sleep of short duration. Chemically related substances with similar though somewhat weaker hypnotic effect include butyl chloral hydrate and chloro-butanol (chloreton). The latter compound is also a mild local anesthetic, antiseptic and preservative.

Disadvantages of chloral hydrate include its pungent odor and bitter taste and its habit-forming tendencies. It is somewhat irritating to mucous membranes unless adequately diluted with water. It should not be used in patients with gastritis. In therapeutic doses, it is probably not toxic to the heart though it should be used with caution in the presence of heart disease. The fatal dose of chloral hydrate is usually considered to be about 10 Gm. though fatalities have resulted from considerably less. Toxic effects include cardiac and respiratory depression. Treatment consists of the use of central nervous system stimulants, intravenous fluids and good nursing care. Introduction of chloral as a hypnotic was due to the fact that Liebreich thought it was decomposed in the body to chloroform and formates, a reaction known to occur in the presence of alkalis. It is now known to circulate unchanged in the body and to be excreted conjugated with glucuronic acid as urochloralic acid.

### PARALDEHYDE

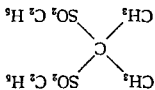


Paraldehyde was introduced as a hypnotic by Cervello in 1882. It is a remarkably safe and rapidly acting drug. Its chief use is in mental institutions to tranquillize excited patients. It has recently been used for preoperative sedation and to produce analgesia and amnesia in childbirth. It is

usually administered orally or rectally. It can be administered intravenously to obtain a prompt effect but this route is not without danger of emboli formation or direct depression of the heart. Intramuscular injection may cause local irritation and tissue damage.

The disadvantages of paraldehyde include its disagreeable taste and the fusel-oil-like smell it imparts to the breath. It is excreted in part by the lungs and should be avoided in bronchitis and pneumonia since it stimulates bronchial secretions. While the drug is of very low toxicity, deaths from idiosyncrasy have been reported. It should be carefully stored since it tends to decompose with the formation of peroxides and an increase in acidity.

### SULFONAL



Sulfonal (sulfonmethane) introduced in 1888, is now little used except in institutional practice. It is particularly useful to sedate cases of chronic mania because of its prolonged depressant action. It is absorbed and excreted slowly and is cumulative with repeated dosage. Toxic effects include depression, ataxia, gastro-intestinal upsets, and kidney irritation. The urine may be a cherry-red color, due to the presence of hematoporphyrin.

Trional (sulfonethylmethane) is related chemically to sulfonal. It is more rapidly absorbed and excreted, and somewhat less toxic.

### BROMIDES

Bromides were first introduced into medicine in 1840 to replace potassium iodide in the treatment of syphilis. They proved ineffective for this purpose but in 1853 their value in the treatment of epilepsy was recognized by Locock.

Their usefulness as hypnotic agents is limited by the fact that their full effect does not develop with a single dose while administration over prolonged periods may lead to chronic bromide intoxication (bromism). Both inorganic (sodium, potassium and ammonium salts) and organic preparations (bromural, carbromal) are available. The latter are generally less toxic, less effective hypnotics and are more expensive. A number of patent headache remedies and cold cures contain bromides and are not infrequently the cause of bromism through self-medication.

Symptoms of bromide poisoning include headache, restlessness, diminished power of concentration, mental confusion and delirium. Bromide rashes occur rather frequently and are probably due to an idiosyncrasy toward the drug. The effect of bromides is determined by the degree of substitution of bromide ions for chloride ions in the body. Decrease of sodium-chloride intake will increase the rate of substitution. Symptoms of toxicity will usually appear before a 40 per cent substitution is attained. Treatment of bromism consists of the oral or intravenous administration of sodium chloride to displace the bromide ion by chloride.

### ANTIEPILEPTIC DRUGS

Antiepileptic drugs are agents used in the treatment of epilepsy. They are frequently referred to as anticonvulsants though they do not necessarily control convulsions other than those of epilepsy. Epileptic seizures are usually classified into three main types on the basis of clinical manifestations and electroencephalographic records.

GRAND-MAL seizures are characterized by convulsions and by the rapid rhythm of the brain waves.

PETIT-MAL seizures consist of temporary lapses of consciousness with immobility or with slight muscular twitching or jerking, usually confined to the eyelids or the brow. The brain records generally show alternating slow and fast rhythms.

PSYCHOMOTOR ATTACKS are characterized by periods of amnesia during which the patient may perform irrational acts. The brain waves are abnormally slow and, unless the patient also suffers from grand- or petit-mal attacks, convulsions rarely occur.

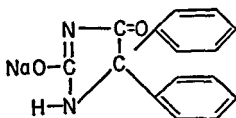
In view of the great differences among the various types of seizures, it is not surprising that none of the existing therapeutic agents is universally satisfactory in the treatment of epilepsy.

With the exception of petit mal, which occurs chiefly in children and which frequently disappears spontaneously, the treatment of epilepsy usually has to be continued indefinitely. The inherent toxicity of a new antiepileptic may therefore not be recognized immediately and a compound should not be deemed nontoxic until it has been used continuously over a period of years. The drug of choice should have no hypnotic, sedative or depressant action. It should not affect adversely the mentality of the patient or interfere with his normal activity. The dosage should be determined by the patient's response, and the drug should be withdrawn if no apparent benefit is derived from it. Furthermore, the preparation should be easy to administer, not unpleasant to take and should be relatively inexpensive.

Bromides as Antiepileptics. The inorganic bromides have been used in the treatment of epilepsy since 1853 but are rapidly being superseded by newer preparations which are less toxic and more effective. The main disadvantage of the bromides is that they tend to hasten the mental deterioration of the patient; in addition, bromism frequently occurs on prolonged administration. The organic bromide preparations are of little value in the treatment of epilepsy. Phenobarbital (luminal) was first used for epilepsy in Germany in 1912. It was introduced into America shortly afterwards but did not receive wide use until after World War I when domestic manufacture of the drug became possible.

sible. It is usually administered orally in tablets but if necessary can be injected intravenously or intramuscularly in the form of the sodium salt. There is some disagreement as to whether it impairs the mentality after prolonged medication. It usually has a sedative and depressant effect causing the patient to feel drowsy and dull. The sudden withdrawal of phenobarbital frequently results in the precipitation of a series of epileptic seizures so that if another drug is to be substituted, phenobarbital should be withdrawn gradually over a period of weeks.

The barbiturate mebaral or prominal (N-methyl, ethylphenyl barbituric acid) is sometimes used in place of phenobarbital, especially in Europe. It is less toxic than phenobarbital and is said to have a less depressing effect.

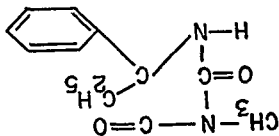


Diphenylhydantoin

Diphenylhydantoin sodium (dilantin) was introduced in 1937 by Putnam and Merritt after a systematic evaluation of the anticonvulsant activity of a large number of drugs by animal experimentation. It is structurally analogous to the barbiturates, being derived from glycolyl urea instead of malonyl urea. In therapeutic dosage, it has a relatively weak hypnotic and sedative action. It is most effective in grand-mal and psychomotor seizures and relatively ineffective in petit mal. It is frequently administered along with phenobarbital, a combination of the two drugs being often more effective than either alone. Even with therapeutic doses, annoying toxic symptoms may occur so that administration should be under careful medical supervision. Toxic effects

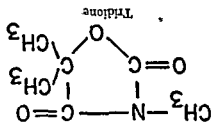
include muscular inco-ordination, gastro-intestinal upsets, skin rashes, hyperplasia of the gums, and occasionally hirsutism. Ordinarily the drug tends to have a stimulating rather than a depressing effect and occasionally may cause hallucinations and delirium.

N-Methyl, phenylethylhydantoin (mesantoin, phenantoin) has recently been introduced for the treatment of grand-mal seizures. It appears to lack some of the undesirable attributes of diphenylhydantoin, such as the production of muscular inco-ordination or gum hyperplasia. However,



there is evidence that some patients develop tolerance to the drug.

Nirvanol (phenylethylhydantoin) was introduced about 1919 as a hypnotic and sedative. It was later widely used in the treatment of chorea. It is little used now because of its toxic manifestations, which include a rise in temperature, skin lesions, edema and eosinophilia.



Trimethadione (tridione). Tridione is a member of a series of drugs which possess hypnotic, analgesic and anti-convulsant properties. Preliminary clinical reports indicate that it may prove of considerable value in petit mal and

psychomotor seizures. It is of little value in the treatment of grand mal, and may even be harmful in this condition. Its most outstanding toxic effects are the production of photophobia and disturbances of color vision. Other toxic symptoms include gastric upsets, skin eruptions, light-headedness and drowsiness. Recently, blood changes have been reported following the use of trimethadione, including fatal cases of aplastic anemia, indicating that the drug should be used cautiously, until its toxic and therapeutic potentialities are more fully evaluated.

**Miscellaneous Agents.** Petit mal is occasionally successfully treated with stimulants such as caffeine and amphetamine sulfate. The production of acidosis or of ketosis and the administration of glutamic acid have also been advocated but the regimens are usually distasteful to the patient and the results for the most part are disappointing.

### PREPARATIONS

Barbital U.S.P.; B.P. 300 mg.

Barbital tablets U.S.P.; B.P. Usually contain 300 mg. barbital.

Barbital sodium (soluble barbital) U.S.P.; B.P.

Barbital-sodium tablets U.S.P.; B.P. Usually contain 300 mg. barbital sodium.

Phenobarbital U.S.P.; B.P. 15-100 mg.

Phenobarbital sodium (soluble phenobarbital) U.S.P.; B.P.

Phenobarbital tablets U.S.P.; B.P.. Usually 15, 30 and 100 mg.

Phenobarbital-sodium tablets U.S.P.; B.P. Usually 30 and 100 mg.

Elixir of phenobarbital U.S.P. Contains not less than 0.37 Gm. or more than 0.43 Gm. phenobarbital in 100 cc.

Pentobarbital sodium U.S.P.; B.P. 100 mg.

Pentobarbital-sodium tablets U.S.P. Usually 30, 50 and 100 mg.

Pentobarbital-sodium capsules U.S.P. Usually 30 and 100 mg.

Alurate N.N.R. 65 mg.

Amytal N.N.R. 100-300 mg.

Dial N.N.R. 100-300 mg.

Probarbital N.N.R. 120-250 mg.

Neonal N.N.R. 50-100 mg.

Nostal N.N.R. 100-300 mg.

Ortal N.N.R. 200-400 mg.

Pernoston N.N.R. 200 mg.

Phanodorn N.N.R. 200 mg.

Sandoptal N.N.R. 200 mg.

Seconal N.N.R. 100-200 mg.

Vinbarbital N.N.R. 100-200 mg.

Chloral hydrate U.S.P.; B.P. 0.6-1.2 Gm.

Butylchloral hydrate N.N.R. 0.3-1.3 Gm.

Chlorobutanol (chlorbutol) U.S.P.; B.P. 0.6 Gm.

Paraldehyde U.S.P.; B.P. 2-8 cc.

Sulfonmethane N.F.; Sulphonol B.P. 0.3-1.2 Gm.

Sulfonethylinmethane N.F.; Methylsulphonol B.P. 0.3-1.2 Gm.

Gm.

Potassium bromide U.S.P.; B.P. 1 Gm.

Sodium bromide U.S.P.; B.P. 1 Gm.

Tablets of potassium bromide B.P. Usually contain 0.3 Gm.

potassium bromide.

Bromural N.N.R. 0.6 Gm.

Carbormal N.N.R.; B.P. 0.3-1 Gm.

Diphenylhydantoin sodium U.S.P. 0.1 Gm.

Diphenylhydantoin sodium capsules U.S.P. Usually 30 and 100 mg.

Trimethadione N.N.R. 0.3 Gm.

## BIBLIOGRAPHY

### GENERAL

Fisher, J. W.: The emergency narcotic treatment of the mental case, Practitioner 152: 108, 1944.



psychomotor seizures. It is of little value in the treatment of grand mal, and may even be harmful in this condition. Its most outstanding toxic effects are the production of photophobia and disturbances of color vision. Other toxic symptoms include gastric upsets, skin eruptions, light-headedness and drowsiness. Recently, blood changes have been reported following the use of trimethadione, including fatal cases of aplastic anemia, indicating that the drug should be used cautiously, until its toxic and therapeutic potentialities are more fully evaluated.

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### PREPARATIONS

Barbital U.S.P.; B.P. 300 mg.

Barbital tablets U.S.P.; B.P. Usually contain 300 mg. barbital.

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Barbital-sodium tablets U.S.P.; B.P. Usually contain 300 mg. barbital sodium.

Phenobarbital U.S.P.; B.P. 15-100 mg.

Phenobarbital sodium (soluble phenobarbital) U.S.P.; B.P.

Phenobarbital tablets U.S.P.; B.P.. Usually 15, 30 and 100 mg.

Phenobarbital-sodium tablets U.S.P.; B.P. Usually 30 and 100 mg.

Elixir of phenobarbital U.S.P. Contains not less than 0.37 Gm. or more than 0.43 Gm. phenobarbital in 100 cc.

Pentobarbital sodium U.S.P.; B.P. 100 mg.

Pentobarbital-sodium tablets U.S.P. Usually 30, 50 and 100 mg.

- Everett, G. M., and R. K. Richards: Comparative anti-convulsive action of 3, 5, 5-trimethylxazolidine-2, 4-dione (tridione), dilantin and phenobarbital, *J. Pharmacol. & Exper. Therap.* 81:402, 1944.
- Glinker, J.: Experiences with luminal in epilepsy, *J.A.M.A.* 75:588, 1920.
- Kozol, H. L.: Epilepsy: treatment with new drug: 3-methyl 5, 5-phenyl-ethyl-hydantoin (phenantoin), *Am. J. Psychiat.* 103:154, 1946.
- Lennox, W. G.: The treatment of epilepsy, *M. Clin. North America* 29:1114, 1945.
- Lennox, W. G.: The petit mal epilepsies. Their treatment with tridione, *J.A.M.A.* 129:1069, 1945.
- Merritt, H. H., and T. J. Putnam: A new series of anti-convulsant drugs tested by experiments on animals, *Arch. Neurol. & Psychiat.* 39:1003, 1938.
- Robinson, L. J.: Evaluation of continued therapy with phenytoin sodium, *Am. J. Psychiat.* 99:231, 1942.
- Waelisch, H., and J. C. Price: Biochemical aspects of glutamic acid therapy for epilepsy, *Arch. Neurol. & Psychiat.* 51:393, 1944.
- Waelisch, H., and J. C. Price: Aplastic Anemia and Tridione, Editorial, *J.A.M.A.* 132:26, 1946.

- Grabfield, G. P.: The use of hypnotics, *J.A.M.A.* 107: 1381, 1936.
- Reitman, F.: *Pharmaco-hypnosis treatment of neuroses*, Practitioner 149: 175, 1942.
- Rice, R. V.: The synthetic organic hypnotics, *J. Am. Pharm. A. (Scient. Ed.)* 33: 289, 1944.
- Solomon, M.: *Insomnia*, *M. Clin. North America* 29: 178, 1945.

#### BARBITURATES

- Dorsey, J. F.: The picrotoxin treatment of barbiturate poisoning, *J. Nerv. & Ment. Dis.* 99: 367, 1944.
- Freireich, A. W., and J. W. Landsberg: Amphetamine (benzedrine) sulfate for acute barbiturate poisoning, *J.A.M.A.* 131: 661, 1946.
- Hambourger, W. E.: A study of the promiscuous use of the barbiturates, their use in suicides, *J.A.M.A.* 112: 1340, 1939.
- Hambourger, W. E.: The promiscuous use of the barbiturates. Analysis of hospital data, *J.A.M.A.* 114: 2015, 1940.
- Tatum, A. L.: The present status of the barbiturate problem, *Physiol. Rev.* 19: 472, 1939.

#### PARALDEHYDE

- Kane, H. F., and G. B. Roth: The relief of labor pains by the use of paraldehyde and benzyl alcohol, *J.A.M.A.* 107: 1710, 1936.

#### BROMIDES

- Gundry, L. P.: Bromide intoxication: report of fifteen cases, *J.A.M.A.* 113: 466, 1939.
- Kane, H. F., and G. B. Roth: Hazards of bromidism in proprietary and uncontrolled hypnotic medication, Council Report, *J.A.M.A.* 115: 933, 1940.
- Kracke, R. R., and W. R. Platt: Bromide intoxication from prolonged self medication with B.C. Headache Powder: report of two cases, *J.A.M.A.* 125: 107, 1944.

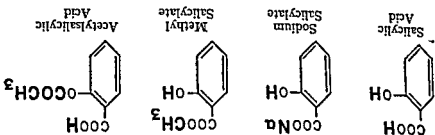
#### ANTIPILEPTIC DRUGS

- DeJong, R. N.: Effect of tridione in the control of psychomotor attacks, *J.A.M.A.* 130: 565, 1946.
- Stern, L., L. Eisenbud and J. Klatell: Analysis of oral reactions to d... 1943.

lution or cause peripheral vasodilation; or by centrally acting drugs which depress the temperature-regulating center. Antipyresis per se is neither necessary nor desirable unless the temperature becomes alarmingly high or the patient is too uncomfortable. In such cases the preferred method of lowering the temperature is by physical means. Hence, although the antipyretic analgesics were for the most part introduced into medicine for their antipyretic action, they are now used almost exclusively for their analgesic action. Certain drugs, such as dinitrophenol, cocaine, the central nervous system stimulants and bacterial toxins, have a pyretic effect similar to that observed after "heat puncture" of the thalamus. The elevation in temperature so produced can be lowered by antipyretic drugs, affording a convenient method of assay of antipyretic potency.

It is generally believed that the heat loss in antipyresis is effected by blood dilution, capillary dilation and increased sweating, while in febrile states the reverse situation obtains. In support of this theory, a lowered blood osmotic pressure has been shown to follow the administration of antipyretics in fever.

### SALICYLATES



The salicylates are the best known and the most widely used analgesics because of their low cost, their comparatively low toxicity and their effectiveness in the alleviation of the pain of headache and neuralgias. The chief members of this series include salicylic acid, sodium salicylate, acetylsalicylic acid (aspirin) and methyl salicylate (oil of winter-

# Antipyretic Analgesics

INTRODUCTION

SALICYLATES

ANTIPYRINE AND

AMINOPYRINE

ACETANILID AND ACETOPHENETIDIN

CINCHOPEN AND

NEOCINCHOPHEN

PREPARATIONS

## INTRODUCTION

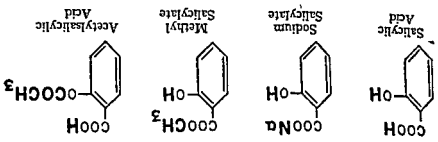
**Analgesics** are agents which relieve pain without producing loss of consciousness. Their site of action may be on the peripheral pain receptors, on the afferent sensory nerves or on the pain centers either in the hypothalamus or in the cortex. The peripherally acting analgesics include the local anesthetics and possibly the counterirritants, although there is some evidence that the pain-relieving action of the latter is a central effect. Drugs which depress the hypothalamic pain centers usually depress the temperature-regulating center as well, and hence are known as *antipyretic analgesics*. The analgesics which act on the pain centers in the cortex include morphine and allied drugs as well as hypnotics which alter the reactions to pain without greatly raising the pain threshold. Conversely, analgesics may have a hypnotic effect by depressing painful stimuli and permitting a relaxation conducive to sleep.

**Antipyretics** are agents which lower the temperature in febrile conditions without materially affecting the normal temperature, at least in therapeutic doses. Antipyresis can be effected by physical means such as cold sponges and baths; by specific chemotherapeutic agents such as the sulfonamides and antibiotics; by drugs which slow the circu-

lution or cause peripheral vasodilation; or by centrally acting drugs which depress the temperature-regulating center. Antipyresis per se is neither necessary nor desirable unless the temperature becomes alarmingly high or the patient is too uncomfortable. In such cases the preferred method of lowering the temperature is by physical means. Hence, although the antipyretic analgesics were for the most part introduced into medicine for their antipyretic action, they are now used almost exclusively for their analgesic action. Certain drugs, such as dinitrophenol, cocaine, the central nervous system stimulants and bacterial toxins, have a pyretic effect similar to that observed after "heat puncture" of the thalamus. The elevation in temperature so produced can be lowered by antipyretic drugs, affording a convenient method of assay of antipyretic potency.

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## SALICYLATES



The salicylates are the best known and the most widely used analgesics because of their low cost, their comparatively low toxicity and their effectiveness in the alleviation of the pain of headache and neuralgias. The chief members of this series include *salicylic acid*, *sodium salicylate*, *acetylsalicylic acid* (aspirin) and *methyl salicylate* (oil of winter-

green). Although salicylic acid itself was first introduced into medicine in 1875, decoctions of willow bark were used as febrifuges for centuries before it was known that their effectiveness was due to the glucoside *salicin*, which yields salicylic acid on hydrolysis. Salicylic acid is irritating to the gastric mucosa and frequently causes nausea and vomiting. It has been replaced for internal use by sodium salicylate and acetylsalicylic acid, introduced in 1899 and 1908, respectively. Externally, salicylic acid is used as a keratolytic and mild antiseptic in dermatologic preparations. Methyl salicylate is a liquid extremely irritating to mucous membranes. It is used as a counterirritant; applied to the skin, it relieves the pain of sprains and afflictions of the joints.

**Salicylate Therapy of Rheumatic Fever.** Since the introduction of salicylic acid into medicine, the salicylates have proved to be the most effective drugs for the treatment of rheumatic fever. Even in low doses these drugs relieve the symptoms of acute rheumatic fever, but it is questionable whether they actually cut down the number of subsequent attacks or affect the prognosis as far as the heart is concerned. Since the cause of rheumatic fever is still obscure, the use of the salicylates in this disease is at present empirical.

Sodium salicylate and acetylsalicylic acid are the two most commonly used drugs in rheumatic-fever therapy. It is now generally believed that the best results are achieved by maintaining a plasma-salicylate level of at least from 25 to 35 mg. per cent, which requires doses of about 10 Gm. per day. Such high doses usually cause some toxic symptoms, but the treatment need not be discontinued unless these become too severe. Administration may be either oral, rectal or intravenous. When sodium salicylate is given orally, sodium bicarbonate may be given to neutralize the acidity and reduce the gastric irritation. However, unless minimal amounts of bicarbonate are used, the salicylate-plasma level will be reduced because of an increased urinary

excretion of salicylates. Acetylsalicylic acid usually causes less gastric upset than sodium salicylate. Since high plasma concentrations are rapidly obtained after oral administration, intravenous administration of salicylates is unnecessary unless the patient is unable to retain oral doses.

**Salicylate Toxicity.** Salicylate toxicity may be chronic, acute or of the nature of an allergic response.

Chronic salicylate poisoning or *salicylism* is not infrequently encountered during the therapeutic use of salicylates. The chief symptoms include headache, dizziness, tinnitus, blurred vision, nausea and vomiting, diarrhea and profuse perspiration. More severe symptoms include hyperventilation, hematemesis and mental disturbances.

Acute salicylate poisoning most often results from the accidental ingestion of oil of wintergreen or the consumption of a large dose of acetylsalicylic acid for suicidal purposes. The symptoms include hyperpnea, hyperpyrexia, ketosis and mental disturbances. Autopsy frequently shows widespread hemorrhages. The fatal dose is variable, patients having been known to survive as much as 30 cc. of oil of wintergreen and 80 Gm. of aspirin, while as little as 4 cc. of oil of wintergreen proved fatal to a one-year-old child. Treatment consists of gastric lavage to remove any unabsorbed drug and the administration of fluids.

Allergic responses to salicylates are occasionally manifested, especially in asthmatic subjects. The symptoms, which on occasion may be quite alarming, include angioneurotic edema of the face and glottis and skin rashes.

The possibility that salicylate therapy may produce hemorrhages by a reduction in blood prothrombin has recently received some attention both clinically and experimentally. It is well known that acetylsalicylic acid may cause gastric bleeding, especially in sensitive individuals. It was first thought that this action was due to an irritant effect since gastroscopic examination may reveal irritation and engorgement of the mucosa around small, undissolved particles of



green). Although salicylic acid itself was first introduced into medicine in 1875, decoctions of willow bark were used as febrifuges for centuries before it was known that their effectiveness was due to the glucoside *salicin*, which yields salicylic acid on hydrolysis. Salicylic acid is irritating to the gastric mucosa and frequently causes nausea and vomiting. It has been replaced for internal use by sodium salicylate and acetylsalicylic acid, introduced in 1899 and 1908, respectively. Externally, salicylic acid is used as a keratolytic and mild antiseptic in dermatologic preparations. Methyl salicylate is a liquid extremely irritating to mucous membranes. It is used as a counterirritant; applied to the skin, it relieves the pain of sprains and afflictions of the joints.

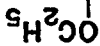
**Salicylate Therapy of Rheumatic Fever.** Since the introduction of salicylic acid into medicine, the salicylates have proved to be the most effective drugs for the treatment of rheumatic fever. Even in low doses these drugs relieve the symptoms of acute rheumatic fever, but it is questionable whether they actually cut down the number of subsequent attacks or affect the prognosis as far as the heart is concerned. Since the cause of rheumatic fever is still obscure, the use of the salicylates in this disease is at present empirical.

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pain-relieving preparations. In 1932, Kracke showed that the condition *agranulocytosis*, first described in Germany in 1922, was associated with drug-therapy and the following year aminopyrine was shown to be one of the chief offending agents. Following this discovery, the use of aminopyrine was forbidden or greatly restricted in many countries.

Agranulocytosis is characterized by a marked fall in leukocyte count, fever, severe sore throat with ulcerations of the mouth and throat and occasionally of the vagina, and prostration. If untreated, death frequently results from secondary infection. The condition seems to be in the nature of an allergic response since attacks frequently bear no relation to dosage or duration of therapy. While most frequently associated with aminopyrine, it has also followed the use of such preparations as the sulfonamides, arsenicals, gold salts, thiouracil and cinchophen. Treatment consists of immediate withdrawal of the drug and administration of penicillin prophylactically or therapeutically to combat any superimposed infections. Adequate nutrition should be maintained and the patient should be protected from possible sources of infection. Pentnucleotide, pyridoxine, liver extract and blood transfusions have been tried but their value has not been established.

# ACETANILID AND ACETOPHENETIDIN

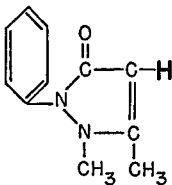


Acetophenetidin

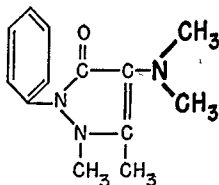
Acetanilid

the drug. Recent work, however, suggests that the salicylates may actually cause hemorrhage by an increase in clotting time. Link and his associates found that dicumerol, the toxic substance in spoiled sweet clover, causes a prothrombopenia in vivo but not in vitro. They suggested that salicylic acid, one of the breakdown products of dicumerol in the body, might be responsible for the prothrombin reduction. Studies on patients have shown that prolonged salicylate therapy does cause the prothrombin level to fall, though there is some difference of opinion as to whether this fall reaches a dangerous level. Since serious hemorrhages have been known to occur during salicylate therapy, it has been suggested that patients whose prothrombin level is appreciably lowered receive prophylactic doses of vitamin K.

#### ANTIPYRINE AND AMINOPYRINE



Antipyrine



Aminopyrine

**Antipyrine and Aminopyrine.** The introduction of salicylic acid into medicine stimulated the search for other synthetic antipyretics. The antipyretic properties of the pyrazolone antipyrine (phenazone) were accidentally discovered by Knorr in 1884, and a few years later the related compound aminopyrine (pyramidon) was introduced. This drug is probably the most effective of the antipyretic analgesics and at one time was used in many proprietary

matic fever and for the relief of pain. It was a common ingredient of patent "cold cures" and arthritis remedies, until its dangerous properties were realized. Although the etiology of gout is not fully understood, cinchophen and its derivative neocinchophen (tolysin) give symptomatic relief and at the same time the uric-acid excretion is increased and the painful uric-acid tophi are reduced or eliminated. The increase in uric-acid excretion has been shown to be due to a selectively increased permeability of the kidney. The value of cinchophen and probably also of the somewhat less toxic neocinchophen is greatly limited by the production of liver damage in susceptible individuals, which may terminate in fulminating yellow atrophy. Jaundice following the use of cinchophen was first reported in 1923, and by 1936, 191 cases had been reported in the literature. Symptoms may develop after very small doses or after the drug has been taken over long periods of time with apparent impunity, or they may develop weeks after the drug has been discontinued. This unpredictable toxicity of cinchophen and related drugs has caused many physicians to believe their potential hazard far outweighs their usefulness and has led to the deletion of cinchophen from the United States Pharmacopoeia.

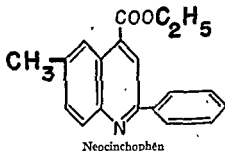
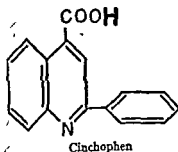
Mild symptoms of cinchophen poisoning resemble those of salicylism. A curious property of some cinchophen preparations is that of producing gastric ulcers in dogs. This does not indicate that cinchophen is an important cause of peptic ulcers in man, since the experimental doses are relatively enormous. It does, however, provide a method for the experimental study of ulcer formation.

Colchicum in the Treatment of Gout. Colchicum is the oldest known remedy for gout and is probably still the drug of choice in the treatment of this disorder. It is prepared from the seeds or the corn of the autumn crocus, *Colchicum autumnale*, the active agent being the alkaloid *colchicine*. The poisonous properties of the autumn crocus were de-

**Acetanilid** (antifebrine) was introduced in 1886, and acetophenetidin (phenacetin) a year later. When first introduced, these drugs were largely used as antipyretics, while acetanilid was also used as an antiseptic on open wounds and ulcers. The large doses employed proved quite toxic; when used in analgesic doses, these drugs are relatively harmless. Both are metabolized in the human body to para-aminophenol, which is probably the active agent but which is too toxic for clinical use, as are also the two "mother substances," aniline and phenol.

Acetanilid and acetophenetidin are commonly used in various proprietary remedies, often in combination with other drugs, such as bromides. Repeated use of these preparations may give rise to habituation and chronic poisoning, characterized by cyanosis, anemia, cardiac weakness and mental confusion. In acute poisoning, there is a rapid fall in body temperature accompanied by symptoms of collapse. Acetanilid and, to a lesser degree, acetophenetidin, produce methemoglobinemia and occasionally sulfhemoglobinemia, which accounts for the cyanosis. It is doubtful whether the methemoglobinemia per se is an important factor in their toxicity. In some species of animals, little or no methemoglobinemia is produced.

#### CINCHOPHEN AND NEOCINCHOPHEN



Cinchophen (atophan) was introduced into medicine in 1908. It is used mainly for the treatment of gout and rheu-

Acetanilid U.S.P. 0.2 Gm.  
 Acetophenetidin U.S.P.; phenacetin B.P. 0.3 Gm.  
 Acetophenetidin tablets U.S.P.; tablets of phenacetin B.P.  
 Usually available as 0.12, 0.2 and 0.3 Gm. tablets.  
 Cinchophen N.F.; B.P. 0.3-1 Gm.  
 Neocinchophen U.S.P. 0.3 Gm.  
 Neocinchophen tablets U.S.P. Usually available as 0.3 and  
 0.5 Gm. tablets.  
 Colchicine U.S.P. 0.5 mg.  
 Colchicine tablets U.S.P. Contain 0.5 mg. colchicine.  
 Tincture of colchicum B.P. Contains approximately 0.03  
 per cent colchicine.  
 Liquid extract of colchicum B.P. Contains approximately  
 0.3 per cent colchicine.  
 Liquid extract of colchicum corn B.P. Contains 0.3 per  
 cent colchicine.

## BIBLIOGRAPHY

### GENERAL

Association for Research in Nervous and Mental Disease,  
 XIII, Pain. Baltimore, Williams & Wilkins, 1943.  
 Dilling, W. J.: Modern therapeutics VII, sedatives and  
 analgesics, Practitioner 144: 189, 1940.  
 Gammon, G. D., and Starr, I.: Studies on the relief of  
 pain by counterirritation. J. Clin. Investigation 20:  
 13, 1941.  
 Hanzlik, P. J.: Actions and Uses of the Salicylates and  
 Cinchophen in Medicine, Baltimore, Williams & Wil-  
 kins, 1927.  
 Wayne, E. J.: Modern therapeutics, XVIII, counter-irri-  
 tation and counter-irritants, Practitioner 145: 422, 1940.  
 Woolley, V. J.: Modern therapeutics, XIV, antipyretics,  
 Practitioner 145: 132, 1940.

### SALICYLATES

Coburn, A. F.: Salicylates therapy in rheumatic fever;  
 a rational technique, Bull., Johns Hopkins Hosp. 73:  
 435, 1943.

scribed by Dioscorides, while its value in the treatment of gout was recognized by the Arabians in the Middle Ages. The mechanism of its action is not known; it does not affect the uric-acid output. It will relieve the pain of acute attacks or abort impending attacks of gout. It is extremely toxic, causing gastro-intestinal irritation and renal damage.

Colchicine arrests mitosis in the metaphase and has proved a useful tool in histologic studies, while its ability to cause doubling of the chromosomes has led to the development of giant-size flowers. It has been tried clinically to arrest neoplastic growths. Results have been disappointing, however, and several fatalities have followed its use.

When applied locally to the epidermis, colchicine produces degenerative cellular changes which lead to cell death. Similar changes are produced by the resin podophyllum, formerly used as a drastic cathartic. Both podophyllum and colchicine have recently been shown to be of value in the treatment of condylomata acuminata.

### PREPARATIONS

*Sodium salicylate* U.S.P.; B.P. 1 Gm.

*Sodium-salicylate tablets* U.S.P.; B.P. Usually available as 0.3 and 0.6 Gm. tablets.

*Acetylsalicylic acid* U.S.P.; B.P. 0.3 Gm.

*Acetylsalicylic-acid tablets* U.S.P. Usually available as 60 mg. and 300 mg. tablets.

*Phenetsal* (acetyl-paraminophenol salicylate) N.N.R. 0.3-1 Gm.

*Salysal* (salicylic ester of salicylic acid) N.N.R. 0.3-0.6 Gm.

*Ethyl salicylate* N.N.R. 0.3-0.6 cc.

*Sal-ethyl carbonate* (carbonic-acid ester of ethyl salicylate) N.N.R. 0.3-1 Gm.

*Phenazone* (antipyrine) B.P. 0.3-0.6 Gm.

*Tablets of phenazone* B.P.

*Aminopyrine* U.S.P.; amidopyrine B.P. 0.3 Gm.

*Aminopyrine tablets* U.S.P. 0.3 Gm. tablets.

Opium is obtained from the dried latex of the poppy, *Papaver somniferum*. The pharmacologic activity of opium is due almost entirely to its morphine content. It is inferior to morphine as an analgesic since it acts less rapidly because of slower absorption. Although it causes more gastric irritation, it has a greater constipating action, and opium preparations, especially camphorated tincture of opium (paregoric) are still widely used in the treatment of diarrhea. Paregoric also has an expectorant action, which is almost negligible in morphine and is useful in the treatment of a dry, hacking cough. Dover's powder, a mixture of ipecacuanha

while that of the narcotine group is on smooth muscle. the morphine alkaloids is on the central nervous system, papaverine. Generally speaking, the predominant action of group of opium alkaloids includes narcotine, narceine and heroin, dihydrid and dionin. The isquinoline or narcotine thebaine and a number of synthetic derivatives such as which also belong the naturally occurring codeine and phenanthrene or morphine group of opium alkaloids, to first isolated by Serturner in 1804. It is a member of the Morphine, the most important constituent of opium, was

## INTRODUCTION

## MORPHINE

## PREPARATIONS

ISONIPECAINE  
METHADON

MORPHINE  
MORPHINE DERIVATIVES

# Morphine and Allied Drugs



- Fashena, G. J. and J. N. Walker: Salicylate intoxication; studies on the effects of sodium salicylate on prothrombin time and alkali reserve, *Am. J. Dis. Child.* 68: 369, 1944.
- Hamill, P.: The therapeutics and toxicology of acetylsalicylic acid, *Practitioner* 142:314, 1939.
- Sable, H. Z.: Toxic reactions following salicylate therapy, *Canad. M.A.J.* 52:153, 1945.

#### ANTIPYRINE AND AMINOPYRINE

- Kracke, R. R.: Relation of drug therapy to neutropenic states, *J. A.M.A.* 111:1255, 1938.

#### ACETANILID AND ACETPHENETIDIN

- Lester, D.: Formation of methemoglobin I; species differences with acetanilide and acetophenetidine, *J. Pharmacol. & Exper. Therap.* 77:154, 1943.
- Payne, S.: Acetanilid poisoning; a clinical and experimental study, *J. Pharmacol. & Exper. Therap.* 53:401, 1935.
- Gross, M.: *Acetanilid; a Critical Bibliographic Review*, New Haven, Hillhouse Press, 1946.

#### CINCHOPHEN

- Bartels, E. C.: Successful treatment of gout, *Ann. Int. Med.* 18:21, 1943.
- Palmer, W. L., and P. S. Woodall: Cinchophen; is there a safe method of administration? *J.A.M.A.* 107:760, 1936.
- Present status of cinchophen and neocinchophen, *J. A.M.A.* 117:1182, 1941.
- Simonds, J. P.: Mode of origin of experimental gastric ulcer induced by cinchophen, *Arch. Path.* 26:44, 1938.

#### COLCHICUM

- Bauer, W., and F. Klemperer: The treatment of gout, *New England J. Med.* 231:681, 1944.
- Brown, W. O., and L. Seed: Effect of colchicine on human tissues. *Am. J. Clin. Path.* 15:189, 1945.
- King, L. S., and M. Sullivan: The similarity of the effect of podophyllin and colchicine and their use in the treatment of condylomata acuminata, *Science* 104:244, 1946.

mechanisms. This reaction is more commonly encountered in women and children than in men.

**Autonomic Nervous System.** Some of the effects of morphine, such as those on pupillary size, on heart rate and on the gastro-intestinal tract, are suggestive of stimulation of the parasympathetic nervous system. There is also experimental evidence to indicate that morphine inhibits the action of choline esterase and acts synergistically with parasympathomimetic drugs. This has led to the suggestion that the actions of morphine are mediated through stimulation of cholinergic synapses. Morphine may cause a hyperglycemia, which is thought to be due to a stimulation of the adrenals leading to a release of epinephrine.

**Sensory Nerve Endings.** Morphine has no effect on the systemic action of the drug following its absorption. Circulation. The effect on the circulatory system of therapeutic doses of morphine is not very marked in man or in laboratory animals. There is usually a moderate slowing of the heart, which may be preceded by a brief increase in rate. The blood pressure may fall slightly; intravenous injection of larger doses may result in circulatory collapse. The effect on the blood vessels is variable though dilation of the vessels of skin and muscles and constriction of visceral vessels are the most usual phenomena. The action seems to be due largely to a direct action on the blood vessels with the vasomotor center playing a minor role.

**Eye.** In man, and in some but not all animals, morphine causes a constriction of the pupil, which in its extreme form results in the "pin-point" pupil characteristic of morphine poisoning. The mechanism of action is not wholly understood; it is probably not entirely a central effect since it can be abolished by sectioning the optic nerve. **Bronchioles.** Constriction of the bronchioles has been demonstrated in animals but large doses are required to elicit the effect. While there is no evidence that bronchial

and opium, is included in the British Pharmacopoeia. It is a powerful diaphoretic and expectorant, used in the treatment of coughs and colds. Opium preparations have been applied locally for the relief of pain but it is doubtful if they are of any value in this respect. Pantopon (omnupon), an artificially prepared mixture of the chief opium alkaloids, can, unlike opium, be administered hypodermically. *It offers no special advantages over morphine.*

#### PHARMACOLOGY

**Central Nervous System.** The action of morphine on the central nervous system varies in different species and to some extent in different individuals. In man, the characteristic effects are depression of the cortical and subcortical structures and of the medulla, and stimulation of the cord. The cortical depression is manifested by an inattentiveness to external stimuli, a dulling of pain sensation, a feeling of well-being and a tendency to sleep. These reactions are the basis of the clinical usefulness of the drug. Respiration is slowed and the cough reflex is depressed. The depressing effect of morphine on respiration is one of the serious drawbacks to its general clinical use. It is a matter of dispute as to whether the effect is due to a primary depression of the respiratory center or secondarily through an increase in the pH of the blood or a reduced need for oxygen because of the decrease in general metabolism. Stimulation of the cord is usually mild in man but may be quite marked in certain animals. Morphine convulsions are strychnine-like in character; there is some evidence that they result from stimulation of certain higher centers as well as centers of the spinal cord.

In the cat family, morphine regularly produces a marked cerebral stimulation instead of the depression characteristically found in man. In some human subjects, however, the drug causes a wild excitement, which is either due to a direct stimulating action or to the depression of inhibitory

the condition by its spasmodic action. It may be used to arrest severe diarrhea and to ease the pain of acute abdominal conditions, provided the diagnosis has been completed and concealment of the pain will not mask the true condition of the patient. Morphine will relieve restlessness and anxiety when these effects are caused by pain and not by such other factors as fear, hysteria or cerebral hypoxia. It should be used with caution in head injuries, however, since it causes an undesirable rise in cerebrospinal-fluid pressure and may mask signs of cerebral damage. Caution is also indicated if the respiration is embarrassed since it may contribute a further depression and if the drug is administered to old persons and children, who usually tolerate it poorly.

Morphine, usually with atropine, is frequently administered from 1 to 2 hours preoperatively to sedate the patient and reduce the amount of anesthetic required. In emergencies, morphine can be given intravenously shortly before the operation is started. Intravenous morphine may also be used to prolong anesthesia towards the end of an operation. Morphine may prolong the induction period with inhalation anesthetics because of the respiratory depression it causes. It will also diminish the pupillary reflex and may contribute to postoperative nausea and vomiting. In obstetrics, morphine with scopolamine is often given to produce "twilight sleep," a state of analgesia and amnesia. The danger of asphyxiation of the child is increased by its use, however, and in the case of premature babies, morphine is contraindicated. Whether the harmful effects are due to the direct action of morphine upon the fetus, or whether the labor mechanism is chiefly involved, resulting in delay in the emptying of the uterus, has been difficult to determine from clinical observation alone. Recent experimental analysis by Cowie<sup>1</sup> and his associates in rab-

constriction occurs in man, morphine should be used with caution in asthma when sensitivity may be increased.

**Intestinal Tract.** Morphine has a marked constipating action due to a delayed emptying of the stomach, decreased activity of the stomach musculature and spasms of the pyloric sphincter. Furthermore, while the tone and the activity of intestinal musculature may be increased, the rate of passage of the contents is decreased. Vomiting may occur because of an initial stimulation of the vomiting center.

**Urinary Tract.** Morphine causes a retention of urine due in part to spasm of the vesical sphincter. It also has an antidiuretic effect, which is apparently mediated through stimulation of the neural lobe of the hypophysis and release of the antidiuretic (pressor) hormone.

#### METABOLISM

The chief route of morphine excretion is by the urine, in which it appears both free and in conjugated form. Traces of morphine are found in the feces and perspiration and possibly also in milk and saliva. A certain amount is destroyed in the body, probably by the liver. It has been shown that the addicted or tolerant dog destroys considerably more morphine than the normal dog and excretes a smaller fraction in the conjugated form, a situation which probably also obtains in man.

#### CLINICAL USES

Morphine is the most effective agent for the relief of pain, but because of its addicting properties it should, in general, only be used when a nonaddicting analgesic will not suffice. It will relieve all types of pain, such as that from coronary occlusion, biliary or renal colic, migraine, pleurisy and severe injuries.

Although morphine relieves the pain of biliary and renal colic by its central analgesic action, it tends to aggravate

Addiction. The main drawback to the use of morphine lies in its addicting properties. The development of drug addiction depends to a great extent on the psychogenic make-up of the individual and the masterfulness of the drug. It is characterized by a development of tolerance toward the drug and the appearance of deranged physiologic processes following the withdrawal of the drug in contrast with the mere psychic craving which follows the withdrawal of habit-forming drugs.

The development of tolerance to morphine depends on the size of the dose and the frequency of administration. Generally speaking, it will develop within three weeks of daily administration of ordinary analgesic doses. Doses must then be progressively increased in order to produce the desired effect. Furthermore, tolerant individuals can withstand doses far greater than those which would be toxic to the non-tolerant individual.

The diagnosis of physiologic dependence to morphine rests on the development of withdrawal symptoms. These symptoms vary according to the individual, being directly related to the severity of the addiction. Symptoms include restlessness, vomiting, mydriasis, tremors, gooseflesh, anorexia, yawning, lacrimation, perspiration, rhinorrhea and fever. Collapse and even death may occur in severe cases. Immediate alleviation of symptoms results from the administration of morphine.

The U. S. Public Health Service maintains a narcotic farm at Lexington, Ky., where patients may apply voluntarily for treatment of drug addiction. Convict addicts are confined and treated in the Federal Prison at Leavenworth. The complete treatment of addiction comprises two stages: disinfection and rehabilitation. The former can be accomplished by slow, rapid or sudden withdrawal of the drug, with or without attempts at substitution with other narcotics. Rehabilitation consists of psychiatric treatment usually disappointing because of the basic inade-

bits, however, revealed a striking prolongation of labor with increased incidence of stillbirths following morphine.

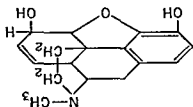
### TOXICITY

Acute morphine poisoning may occur from accidental or criminal overdosage or in individuals who tolerate the drug poorly. It is characterized by extreme miosis ("pin-point" pupils), markedly slowed respiration, cold, clammy skin and coma. Treatment consists of prolonged artificial respiration, if possible with oxygen. The patient should not be exhausted by stimulant drugs or physical means such as "walking the floor." Morphine re-excreted into the stomach can be removed by gastric lavage and reabsorption from the bowel can be prevented by colonic lavage; the amount of morphine removed by these means is insignificant, however, except when the drug has been taken by mouth. Supportive treatment includes the use of intravenous glucose and the maintenance of body temperature. Good nursing care is of the utmost importance.

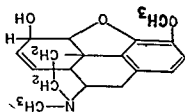
The subcutaneous injection of morphine is ordinarily followed by a rapid response. When the circulation is inadequate, as in shocked patients, especially those exposed to cold, absorption may be delayed and the continued pain may lead to the administration of one or more additional doses of morphine. When shock treatment is instituted and the circulation improves, the several doses of morphine may be absorbed simultaneously and may act as one massive dose. The symptoms and treatment of this delayed poisoning are those of acute morphine poisoning. Prophylactic measures include intramuscular injection with massage of the site of administration in all shocked or hypotensive patients. If circumstances permit, the intravenous administration of small doses of the drug will insure rapid development of the full effects and will obviate the danger of delayed poisoning.

grain of codeine in 1 ounce. International problems of opium regulation are governed by the Hague Convention of 1912 and the Geneva Conventions of 1925 and 1931. The League of Nations maintained an Opium Advisory Committee, which met annually to discuss opium control. This function has been assumed by the United Nations organization.

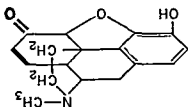
## MORPHINE DERIVATIVES



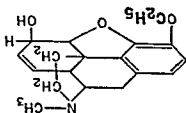
Morphine



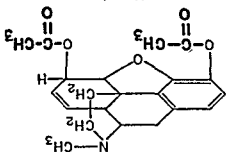
Codeine  
(Methylmorphine)



Dilaudid  
(Dihydromorphinone)



Dionin  
(Ethylmorphine)



Heroin  
(Diacetylmorphine)

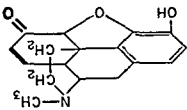
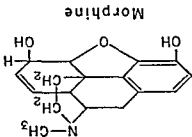


quacies in the personality of the addict. Intensive studies are being carried out under the direction of the Committee of Drug Addiction of the National Research Council by the U. S. Public Health Service and a number of collaborating institutions, with a view to determining the exact nature of addiction and to obtaining nonaddicting morphine substitutes. As yet, no comparable analgesic agent has been developed which does not have addicting tendencies. Among the most promising derivatives studied are *metapon* (methyldihydromorphinone) and *desomorphine* (dihydrodesoxymorphine-D). *Desomorphine* has an effective analgesic action in very small doses but its action is of shorter duration and less reliable than that of morphine, while its addicting properties are comparable to those of morphine. *Metapon* is an excellent analgesic for the control of chronic pain; tolerance and dependence are developed more slowly than with morphine and are apparently lost quite rapidly during short periods of abstinence. It is not satisfactory for pre-anesthetic medication, however, since it has only a slight hypnotic effect and occasionally causes severe respiratory depression when used in conjunction with inhalation anesthetics.

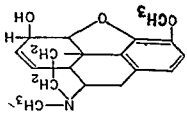
The production, manufacture and distribution of addicting drugs is regulated by the Harrison Narcotic Act, passed in 1914, and its several amendments. The act covers "opium and coca leaves, and compounds, manufactures, salts, derivatives or preparations thereof." Such drugs can only be prescribed by physicians possessing a narcotics license, which must be renewed yearly. All prescriptions must be made on official narcotic order forms and must bear the physician's license number. They are not refillable. Certain preparations containing only small amounts of restricted drugs are exempt, as are preparations for external application only, except for those containing cocaine. Exempt preparations include those containing no more than 2 grains of opium,  $\frac{1}{4}$  grain of morphine,  $\frac{1}{8}$  grain of heroin or 1

grain of codeine in 1 ounce. International problems of opium regulation are governed by the Hague Convention of 1912 and the Geneva Conventions of 1925 and 1931. The League of Nations maintained an Opium Advisory Committee, which met annually to discuss opium control. This function has been assumed by the United Nations organization.

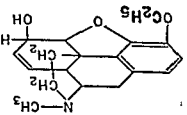
## MORPHINE DERIVATIVES



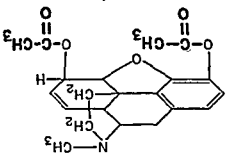
Dilaudid (Dihydromorphinone)



Codeine (Methylmorphine)



Dionin (Ethylmorphine)



Heroin (Diacetylmorphine)

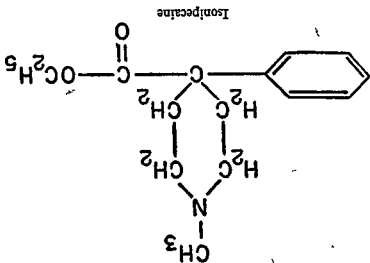
Codeine was first isolated from opium in 1832 by Robiquet and came into general clinical use in 1880. It is prepared commercially largely by the methylation of morphine, only small amounts being obtained from opium during the extraction of morphine. It is used mainly for the relief of cough and of moderately severe pain. It has definitely weaker analgesic, respiratory, depressant, emetic and intestinal effects than morphine. It is less addictive than morphine, though, in some cases, withdrawal symptoms may be as severe as those following the withdrawal of morphine. Codeine causes less euphoria than morphine and is more costly in addiction-sustaining amounts. There is a cross tolerance between the two drugs, large doses of codeine relieving the withdrawal symptoms of morphine addicts.

Dihydromorphinone hydrochloride (dilaudid) was introduced into Germany by Krehl in 1926. Its analgesic potency is about four times that of morphine though its duration of action is shorter. While it is an efficient substitute for morphine, it has no therapeutic advantages and has equal or greater addicting properties.

Heroin (diacetylmorphine, diamorphine) was introduced into Germany in 1898 by Dreser. At first considered to be a nonaddicting substitute for morphine and codeine, it was later found to be more addictive than morphine and its manufacture and importation is prohibited in the United States.

Ethylmorphine (dionin) has an analgesic action intermediate between that of codeine and morphine and has similar addicting properties. It is used chiefly in ophthalmology in inflammatory conditions. It stimulates the vascular and lymphatic circulations by a dilating effect on the vessels and has a local anesthetic action on the conjunctival sac.

ISONIPECCAIN



Isonipeccaine (demerol mepredine) is one of the most successful substitutes for morphine. It was synthesized in Germany in 1939 by Eisleb and Schaumann, who were searching for new compounds with an atropine-like action. They found that this substance had, in addition to parasympatholytic properties, a direct spasmolytic effect on smooth muscle similar to that of papaverine and a central analgesic and sedative effect like that of morphine. The drug is known in Germany as dolantin; in Great Britain the official name is pethidine.

Isonipeccaine relieves all types of pain, being only slightly less effective than morphine. The dose is approximately ten times that of morphine but the drug is much less toxic and is quite rapidly metabolized in the body. It is much less liable to cause addiction than morphine but since it does possess addicting properties it has recently come under the scope of the Federal narcotic law.

Isonipeccaine has a relaxing action on the gut musculature but does not delay the passage of the gut contents and does not have the constipating action of morphine. It is probably more efficient than morphine for the relief of

Codeine was first isolated from opium in 1832 by Robiquet and came into general clinical use in 1880. It is prepared commercially largely by the methylation of morphine, only small amounts being obtained from opium during the extraction of morphine. It is used mainly for the relief of cough and of moderately severe pain. It has definitely weaker analgesic, respiratory, depressant, emetic and intestinal effects than morphine. It is less addictive than morphine, though, in some cases, withdrawal symptoms may be as severe as those following the withdrawal of morphine. Codeine causes less euphoria than morphine and is more costly in addiction-sustaining amounts. There is a cross tolerance between the two drugs, large doses of codeine relieving the withdrawal symptoms of morphine addicts.

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Its analgesic action is quite similar to that of morphine but it apparently causes less gastro-intestinal distress and respiratory depression. It is not as satisfactory as morphine as a preanesthetic agent since it causes little or no euphoria and leaves the patient apprehensive. There is no information yet as to whether prolonged use leads to tolerance or addiction, and until these questions are answered, cautious use of the drug is advisable.

## PREPARATIONS

Powdered opium U.S.P.; B.P. Granulated opium U.S.P. Contains approximately 10 per cent anhydrous morphine. 60 mg.

Opium tincture (laudanum) U.S.P.; B.P. Contains approximately 1 per cent opium. 0.6 cc.

Camphorated opium tincture (paregoric) U.S.P.; B.P. Contains approximately 0.04 per cent anhydrous morphine. 4 cc.

Morphine sulfate U.S.P.; B.P. Morphine hydrochloride, B.P. Morphine tartrate B.P. 10 mg.

Morphine-sulfate tablets U.S.P. Usually available in 5, 8, 10, 15, and 30 mg. amounts.

Morphine injection U.S.P. Usually contains 10, 15, 20 or 30 mg. morphine salt in 1 cc.

Codeine B.P. 30 mg.

Codeine phosphate U.S.P.; B.P. Codeine sulfate U.S.P. 30 mg.

Codeine-phosphate tablets U.S.P.; B.P. Codeine sulfate tablets U.S.P. Usually available in 15, 30 and 60 mg. amounts.

Dihydromorphine hydrochloride U.S.P. 2 mg.

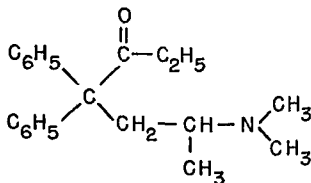
Dihydromorphine-hydrochloride tablets U.S.P. Usually available in 1, 2 and 4 mg. amounts.

N-vinylmorphine hydrochloride U.S.P. 15 mg.

biliary and urinary colic since it has a direct spasmolytic effect in addition to a central analgesic action. It is also of value in the treatment of asthma because of its relaxing action on the bronchioles. It has recently been introduced for preanesthetic medication and for obstetric analgesia. It is said to be superior to morphine since it causes little or no respiratory depression, it decreases salivary secretion and does not markedly interfere with the pupillary reflex, and it is said to cause less postoperative nausea and vomiting than morphine. It has been claimed to hasten labor by a direct relaxing action on the uterine cervix. It must be combined with barbiturates or scopolamine if amnesia as well as analgesia is desired.

Mild toxic actions following the use of isonipecaine include giddiness, dryness of the mouth, nausea and vomiting, sweating, headache and anxiety. More severe toxic effects resemble those of atropine poisoning.

#### METHADON



Methadon

Recently, a new synthetic analgesic developed in Germany has given promising clinical results in a limited series of cases. The drug is the hydrochloride of 1, 1-diphenyl-1-(2-dimethylaminopropyl)-2-butanone and is known as methadon, amidone, dolophine or 10820.

- Pearman, R. O.: Intravenous use of morphine sulfate, *Am. J. Surg.* 61:423, 1943.
- Presman, D., and S. Schotz: A critical analysis of the use of intravenous morphine, *Anesthesiology* 4:53, 1943.
- Schmidt, C. F., and A. E. Livingston: The action of morphine on the mammalian circulation, *J. Pharmacol. & Exper. Therap.* 47:411, 1933.
- Slaughter, D.: New concepts of morphine analgesia, *Anesthesiology* 5:508, 1944.
- Snyder, F. F., and E. M. K. Gelling: Action of morphine in obstetric analgesia, *Am. J. Obst. & Gynec.* 45:604, 1943.

## ISONITRECAINE

- Batterman, R. C., and C. K. Himmlsbach: Demerol—new synthetic analgesic—a review of its present status and comparison with morphine, *J.A.M.A.* 122:222, 1943.
- von Eisleb, O., and O. Schumann: Dolantin, ein neuartiges Spasmolytikum und Analgetikum (chemisches and pharmakologisches), *Deutsche Med. Wochenschr.* 65:967, 1939.
- Himmlsbach, C. K.: Studies of the addiction liability of "demerol" (D-140), *J. Pharmacol. & Exper. Therap.* 79:5, 1943.
- Noth, F. H., H. H. Hecht and F. F. Vonkman: Demerol—a new synthetic analgesic, spasmolytic and sedative agent, II, clinical observations, *Ann. Int. Med.* 21:17, 1944.
- Roby, C., and W. R. Schumann: Demerol (S-140) and scopolamine in labor—a preliminary report, *Am. J. Obst. & Gynec.* 45:318, 1943.
- Rovenstine, E. A., and R. C. Batterman: The utility of demerol as a substitute for the opiates in preanesthetic medication, *Anesthesiology* 4:126, 1943.
- Vonkman, F. F., F. H. Noth and H. H. Hecht: Demerol: a new synthetic analgesic, spasmolytic and sedative agent, I, pharmacologic studies, *Ann. Int. Med.* 21:7, 1944.



Diamorphine hydrochloride B.P. (Diacetylmorphine or heroin). 2-8 mg.

Meperidine hydrochloride N.N.R. 0.05-0.1 Gm.

## BIBLIOGRAPHY

### GENERAL

Indispensable use of narcotics, J.A.M.A. 119:338, 1942.

### MORPHINE

Adams, E. W.: Drug addiction, New York, Oxford, 1937.  
Adams, E. W.: Studies on drug addiction, Pub. Health Rep., Supplement 138, Washington, U. S. Government Printing Office, 1938.

Adams, E. W.: The Pharmacology of the opium alkaloids, Parts 1 and 2, Pub. Health Rep., Supplement No. 165, Washington, U. S. Government Printing Office.

Beecher, H.K.: Delayed morphine poisoning in battle casualties, J.A.M.A. 124:1193, 1944.

Bodo, R. C., F. W. Cotui and A. E. Benaglia: Studies on the mechanism of morphine hyperglycemia; the rôle of the adrenal glands, J. Pharmacol. & Exper. Therap. 61:48, 1937.

Gross, E. G., and V. Thompson: The excretion of a combined form of morphine in tolerant and nontolerant dogs, J. Pharmacol. & Exper. Therapy. 68:413, 1940.

Lee, L. E., Jr.: Studies of morphine, codeine and their derivatives, XVI, clinical studies of morphine, methyl-dihydromorphinone (metopon) and dihydrodesoxymorphine-d (desmorphine), J. Pharmacol. & Exper. Therap. 75:161, 1942.

Mengert, W. F.: Morphine sulfate as an obstetric analgesic, a clinical analysis, Am. J. Obst. & Gynec. 44:888, 1942.

McCrea, F. D., G. S. Eadie and J. E. Morgan: The mechanism of morphine miosis, J. Pharmacol. & Exper. Therap. 74:239, 1942.

Oberst, F. W.: Studies on the fate of morphine, J. Pharmacol. & Exper. Therap. 74:37, 1942.

Oberst, F. W.: Free and bound morphine in the urine of morphine addicts, J. Pharmacol. & Exper. Therap. 69:240, 1940.

# Central Nervous System Stimulants

INTRODUCTION	NIKETHAMIDE
STRYCHNINE	CAFFEINE
PICROTOXIN	AMPHETAMINE AND RELATED COMPOUNDS
METRAZOL	MISCELLANEOUS PREPARATIONS
PREPARATIONS	

Central nervous system stimulants may act primarily as spinal stimulants (strychnine), medullary stimulants (picROTOXIN, metrazol and nikethamide) or cerebral stimulants (caffeine and amphetamine). In large doses, they induce convulsions, which, with the exception of the metrazol-induced convulsions used in shock therapy of mental disorders, are of toxicologic importance only. In smaller doses, they act as anaesthetics or restoratives and are capable of antidoling depression.

## STRYCHNINE

Strychnine, the principal alkaloid obtained from the seeds of *Strychnos nux vomica*, was first isolated by Pelletier and Cavenou in 1818. It acts chiefly on the spinal cord, increasing reflex excitability. It has therefore no direct stimulatory action but sensitizes the nervous system to external stimuli. It has little or no clinical value as a central nervous system stimulant since most depressants act primarily by depression of the medullary centers and strychnine stimulates the medulla only in convulsive doses. On the other hand, the depressant drugs are antidotes to strychnine poisoning since these drugs usually depress the spinal cord before depressing the medulla. The stimulatory action of strychnine

## METHADON

- Scott, C. C., K. G. Kohlstaedt and K. K. Chen: Comparison of the pharmacologic properties of some new analgesic substances, *Anesth. & Analg.* 26:12, 1947.
- Scott, W. W., H. M. Livingstone, J. J. Jacoby and G. R. Broberg: Early clinical experience with dolophine (No. 10820), *Anesth. & Analg.* 26: 18, 1947.

and the East Indies. The fruit of this plant, known as fish berry, levant berries or *Cocculus indicus*, is used by natives to stupefy fish.

Small doses of picrotoxin stimulate the medulla and probably also the cortex. The spinal cord is stimulated to a lesser extent. Picrotoxin acts as a pharmacologic antidote to drugs which depress the respiratory center and is the agent of choice in the treatment of severe barbiturate depression (see Chapter 7). It is contraindicated in morphine poisoning, however, because morphine appears to sensitize the cord to picrotoxin so that convulsions appear before respiratory stimulation is apparent.

The value of picrotoxin as an antidote to depressant drugs was first demonstrated experimentally in 1875. During the following years it was used to a limited extent clinically to combat overdoses of hypnotics and general anesthetics but did not gain widespread recognition until its efficacy in barbiturate poisoning was demonstrated by Maloney, Ritch and Tatum in 1931. Picrotoxin has also been used to produce convulsions in the shock treatment of mental disorders. It is effective in lower doses than metrazol and is said to cause less apprehension. However, the onset of convulsions is often delayed and the action of the drug is less predictable than that of metrazol. In the past, picrotoxin has been added to beer for its bitter and intoxicating properties. It has also been used externally as an antiparasitic agent. Its extreme toxicity makes these uses dangerous.

Overdoses of picrotoxin lead to a depression of the central nervous system and the sequence of events in picrotoxin poisoning is convulsions, confusion and unconsciousness. In using picrotoxin as a respiratory stimulant, care should be taken to avoid convulsions, which may lead to further depression of the center. Picrotoxin can be effectively antidoted by intravenously administered barbiturates.

on the higher centers is usually not very marked, though in some individuals it sharpens visual and auditory acuity.

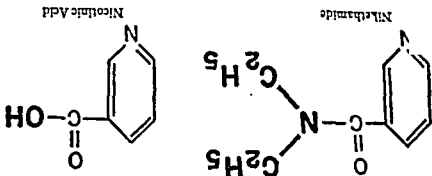
Strychnine poisoning not uncommonly results from criminal activities or accidental ingestion of strychnine-containing plants or medicinal preparations. Consciousness is retained despite severe tonic convulsions which affect all muscles of the body. In the human, the body is arched back in the position of opisthotonus. The convulsions are provoked by external stimuli, hence the patient must be kept completely quiet and in a darkened room, and no attempt should be made to pass a stomach tube or otherwise to disturb the patient. Short-acting barbiturates, administered intravenously, are probably the most effective antidotes. Death from strychnine poisoning usually results from respiratory failure due to exhaustion of the respiratory center.

The manner in which strychnine increases reflex excitability is not fully understood. It has been found that small doses of strychnine inhibit the action of choline esterase, the enzyme which destroys acetylcholine. This suggests that the mode of action of strychnine might be somewhat analogous to that of physostigmine with the primary effect being located in the central nervous system rather than in the autonomic nervous system.

Brucine, an alkaloid obtained during the preparation of strychnine, has very weak strychnine-like pharmacologic properties. Preparations of nux vomica, strychnine or brucine are used largely as tonics; they stimulate the appetite because of their bitterness and increase the flow of salivary and gastric secretions. Strychnine is frequently included in proprietary cathartics, allegedly to increase the tone of the intestinal musculature.

### PICROTOXIN

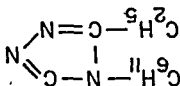
Picrotoxin is a glycoside obtained from the seed of *Anamirta paniculata*, a climbing plant indigenous to Malabar



## NIKETHAMIDE

effective in smaller doses than metrazol and can be given either intravenously or intramuscularly. It is said to cause less apprehension in patients.

Triazol 156

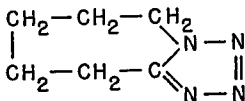


Triazol 156 (azoman, hexazole) has somewhat similar pharmacologic properties to metrazol and has been quite extensively used in Europe for convulsant therapy. It is

tal muscles. curare, which greatly diminish the contractions of the skeletal muscles. The administration of purified preparations of spine by the administration of the extremities or rected from fractures or dislocations of the extremities or nary disease or spinal injuries. The patient may be pro-administered in the presence of cardiovascular or pulmo-the severity of the convulsions, metrazol should not be the rapid destruction of the drug by the liver. Because of in nature and of comparatively short duration because of venous administration of the drug. They are mainly clonic-vulsions usually occur within one minute after the intra-probably safer electrical convulsive therapy. Metrazol con-it has recently been largely replaced by the simpler and

## METRAZOL

Metrazol (leptazol, cardiazol) was introduced into Germany by Schmidt, Hildebrandt and Krehl in 1925 as a water-soluble substitute for camphor, which was held in considerable repute on the Continent as a respiratory and cardiac stimulant. It was first known as cardiazol, a somewhat misleading name, since the drug in therapeutic doses has little or no effect on the coronary flow, the heart rate or the blood pressure. Its chief pharmacologic action is



Metrazol

stimulation of the medullary centers. It is an effective antidote to respiratory depressants though inferior to picrotoxin in severe barbiturate poisoning. Like picrotoxin, it should be avoided in morphine poisoning because of the danger of inducing spinal convulsions.

Metrazol has been used extensively in the drastic shock treatment of certain mental diseases, principally schizophrenia and depressive psychoses. The use of convulsant drugs in mental disease was initiated by de Meduna in 1933. He reasoned that since schizophrenia and epilepsy seldom occurred together, there was a biologic incompatibility between the two disorders. He sought, therefore, to induce epileptiform convulsions in schizophrenic patients, at first by the intramuscular injection of camphor and later by the intravenous injection of metrazol, which produced much more prompt and reliable convulsions. Although de Meduna's hypothesis is not generally accepted as correct, the treatment has proved of considerable value, although

It is of questionable value as an antidote for depressant poisons, except in cases of mild alcohol or mild morphine poisoning.

Caffeine is comparatively nontoxic. Excessive doses lead to insomnia and nervousness, while its diuretic action is of some disadvantage in its use as a stimulant. The related compounds, theobromine and theophylline, have qualitatively similar stimulatory actions. Much larger doses are required, however, and these drugs are more widely used as diuretics, since their comparative freedom from central effects makes them more useful than caffeine. The innocuousness of caffeine is attested to by the wide consumption of caffeine-containing drinks for their palatability and mildly stimulating properties. The average cup of tea or coffee contains approximately 0.1 Gm. of caffeine. Excessive use of these beverages may be harmful in patients susceptible to peptic ulcer since caffeine has been shown to stimulate the flow of gastric juices in man.

## AMPHETAMINE AND RELATED COMPOUNDS

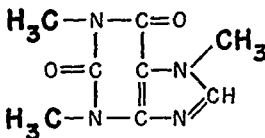
The shortcomings of the camphor substitutes, mefrazol and nikethamide, encouraged the search for more effective central nervous system stimulants and led to the introduction of amphetamine and of various sympathomimetic amines with analeptic properties. Of the latter group of compounds, amphetamine (benzedrine) was the first to receive extensive clinical use. This drug was first introduced as a nasal decongestant (see Chapter 11). Its marked stimulatory action on the central nervous system soon became apparent, and in 1935 the nonvolatile sulfate salt was used successfully as an analeptic in amyotal anesthesia. It is now used widely in the treatment of narcolepsy and in various psychogenic depressive states. The establishment of the value of amphetamine as a stimulant led to studies of related compounds and to the introduction of d-desoxyephedrine (methedrine, pervitin)



Nikethamide (coramine) was introduced into Germany in 1924 as a substitute for camphor. It is much less effective as an analeptic than picrotoxin or metrazol and is of little value in the treatment of severe respiratory depression. It may increase the rate of coronary blood flow, and it is claimed to be of value in combatting postoperative depression and traumatic shock by maintaining the intramuscular pressure and venous blood pressure and flow. It is comparatively nontoxic, and up to 30 cc. of the 25 per cent solution have been given without ill effects.

Nikethamide is related chemically to nicotinic acid and, like the latter, is capable of alleviating the symptoms of pellagra and black tongue (see Chapter 22).

#### CAFFEINE



Caffeine

Caffeine is an alkaloid which may be prepared synthetically or obtained from various plant sources, including coffee seeds, tea leaves, maté, guarana and kola. The main commercial source of caffeine is damaged tea.

Caffeine is a mild cerebral stimulant, its action on the lower centers being inconsequential. It tends to facilitate mental and muscular effort and to diminish drowsiness and motor fatigue. It has been suggested that caffeine increases the capacity for muscular activity by decreasing the threshold for response to acetylcholine at the neuromuscular junction. Caffeine frequently relieves the pain of mild headaches, possibly by lowering the cerebrospinal-fluid pressure.

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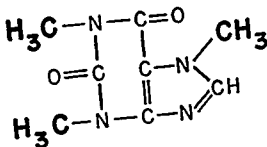
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and of dexedrine, the dextrorotatory component of the racemic amphetamine. Dexedrine elicits more marked central effects than its levorotatory isomer or the racemic mixture, although its peripheral effects are less marked. Comparative studies indicate that the central nervous system stimulant effect of these drugs is not correlated with their sympathomimetic activities.

In the normal subject, amphetamine usually gives a feeling of increased well-being, mental stimulation, lessened fatigue and even euphoria. In a few individuals, depression of mood occurs. The stimulating effects of the drug led to its indiscriminate use in the form of "pep pills," which were especially popular with students on the eve of examinations. Several fatalities were reported following such unsupervised use, and, as a result, restrictions have been placed on its sale in many areas.

Amphetamine sulfate has been widely advocated for the treatment of obesity, since it depresses the appetite and maintains the patient's feeling of well-being despite a low caloric intake. However, directly the drug is withdrawn, the appetite returns in full and unless a new food pattern has been established the patient generally is unwilling to adhere to his former diet. Furthermore, there is a danger of habit formation, especially since the type of patient requiring amphetamine will be one prone to become habituated to the drug. It has also been used as an adjunct to psychotherapy in the treatment of chronic alcoholism.

Toxic manifestations of amphetamine overdosage include irritability, anxiety, insomnia, dizziness, headache and nausea. Several cases of collapse, evidently due to idiosyncrasy, have been reported. Tolerance may develop after prolonged medication; however, moderate doses have been taken over a period of years for the treatment of narcolepsy, without any apparent ill effects.

Dexedrine and d-desoxyephedrine may be used in place of amphetamine when central stimulation is required. They

are effective in somewhat lower dosage. D-desoxyephedrine was developed in Germany, where it was used quite extensively by the army and the air force to produce a temporary state of alertness.

### MISCELLANEOUS PREPARATIONS

Alpha-lobeline, the principal alkaloid of *Lobelia inflata* Linne (Indian tobacco), and various cyanide preparations have been recommended as respiratory stimulants in narcotic poisoning and in asphyxia neonatorum because of their stimulatory action on the carotid body. Their effects are unreliable and fleeting, however, and are obtained only with nearly toxic doses.

Ammonia water and camphor have long enjoyed a popular reputation as stimulants. Ammonia water, when given orally, or when its vapors are inhaled, stimulates the vasomotor center reflexly by stimulation of the chemoreceptors of the carotid body, but its action is evanescent. The value of camphor as a respiratory or cardiac stimulant is doubtful and quite unreliable.

### PREPARATIONS

Strychnine sulfate U.S.P. 2 mg.  
Strychnine-sulfate tablets U.S.P. Usually of 0.6, 1.0, 1.2, 1.5 and 2 mg. amounts.  
Strychnine hydrochloride B.P. 2 mg.  
Solution of strychnine hydrochloride B.P. Contains 1 per cent strychnine.  
Picrotoxin U.S.P. (Dose determined by needs of the patient.)  
Picrotoxin injection U.S.P. Usually available in ampuls containing 3 mg. picrotoxin in 1 cc. isotonic sodium chloride. Metrazol N.N.R.; leptazol B.P. 0.06-0.3 Gm.  
Injection of leptazol B.P. Contains 10 per cent leptazol.  
Injection of nikethamide B.P.; N.N.R. 25 per cent solution of nikethamide in distilled water. 1-4 cc.

Caffeine U.S.P.; B.P. 0.2 Gm.

Citrated caffeine U.S.P. A mixture of approximately equal amounts by weight of caffeine and citric acid. 0.3 Gm.

Caffeine and sodium benzoate. U.S.P.; B.P. A mixture of approximately equal amounts by weight of caffeine and sodium benzoate. 0.5 Gm.

Caffeine and sodium-benzoate injection U.S.P. Usually available as capsules containing 0.25 Gm. and 0.5 Gm. in 2 cc.

Amphetamine sulfate B.P.; N.N.R. 5-10 mg.

## BIBLIOGRAPHY

### GENERAL

Burn, J. H.: Analeptics and sympathomimetic substances, *Brit. M. J.* 1: 599, 1939.

Hazleton, L. W.: The present status of analeptics, *J. Am. Pharm. A. (Scien. Ed.)* 33: 65, 1944.

Lim, K. T., and F. F. Snyder: The effect of respiratory stimulants in the newborn infant, *Am. J. Obst. & Gynec.* 50: 146, 1945.

### STRYCHNINE

Aikman, J.: Strychnine poisoning in children, *J.A.M.A.* 95: 1661, 1930.

Anderson, W. F.: The tonic action of strychnine, *Brit. M. J.* 1: 360, 1944.

Drusser de Barenne, J. G.: The mode and site of action of strychnine in the nervous system, *Physiol. Rev.* 13: 325, 1933.

Travell, J., and H. Gold: Mechanism of action of strychnine on respiration, *J. Pharmacol. & Exper. Therap.* 53: 169, 1935.

### PICROTOXIN

Maloney, A. H., R. H. Fitch and A. L. Tatum: Picrotoxin as an antidote in acute poisoning by the shorter acting barbiturates, *J. Pharmacol. & Exper. Therap.* 41: 465, 1931.

## METRAZOL

- Bennett, A. E.: Preventing traumatic complications in convulsive shock therapy by curare, J.A.M.A. 114:322, 1940.
- Ebaugh, F. G.: A review of the drastic shock therapies in the treatment of the psychoses, Ann. Int. Med. 18:279, 1943.
- de Meduna, L.: New methods of medical treatment of schizophrenia, Arch. Neurol. & Psychiat. 35:361, 1936.
- Walk, A., and W. Mayer-Gross: Observations on convulsion therapy with triazol 156, J. Ment. Sc. 84:637, 1938.

## NIKETHAMIDE

- Gunther, L., H. Engelberg and L. Strauss: Intramuscular pressure, II, the venopressor mechanism in shock-like conditions and the effects of various drugs, Am. J. M. Sc. 204:271, 1942.
- Smith, D. T., G. Margolis and L. H. Margolis: The black-tongue curative effect of pyridine- $\beta$ -carboxylic acid diethylamide (coramine), J. Pharmacol. & Exper. Therap. 68:458, 1940.

## CAFFEINE

- Foltz, E. E., A. C. Ivy and C. J. Barborka: The influence of amphetamine (benzedrine) sulfate, d-desoxyephedrine hydrochloride (pervitin) and caffeine upon work output and recovery when rapidly exhausting work is done by trained subjects, J. Lab. & Clin. Med. 28:603, 1942-1943.
- Huidobro, R. and E. Amenabar: Effectiveness of caffeine (1, 3, 7, trimethylxanthine) against fatigue, J. Pharmacol. & Exper. Therap. 84:82, 1945.

- Roth, J. A., A. C. Ivy and A. J. Atkinson: Caffeine and "peptic" ulcer: relation of caffeine and caffeine-containing beverages to the pathogenesis, diagnosis and management of "peptic" ulcer, J.A.M.A. 126:814, 1944.
- Albrecht, F. K.: The use of benzedrine sulfate in obesity, Ann. Int. Med. 21:983, 1944.

## AMPHETAMINE AND RELATED PREPARATIONS

- Bakst, H. J.: Daily use of benzedrine sulfate over a period of nine years—report of a case, U. S. Nav. M. Bull. 43:1228, 1944.



- Davidoff, E.: A comparison of the stimulating effect of amphetamine dextroamphetamine and dextro-N-methyl amphetamine (dextro-desoxyephedrine), *M. Rec.* 156: 422, 1943.
- Ivy, A. C., and F. R. Goetzel: D-desoxyephedrine, a review. *War Med.* 3: 60, 1943.
- Ivy, A. C., and L. R. Krasno: Amphetamine (benzedrine) sulfate—a review of its pharmacology, *War. Med.* 1: 15, 1941.
- Norman, J., and J. T. Shea: Acute hallucinosis as a complication of addiction to amphetamine sulfate: report of a case, *New England J. Med.* 233: 270, 1945.
- Reifenstein, E. C., Jr., and E. Davidoff: Intravenous benzedrine sulfate as an antagonist to intravenous soluble amytal, *Proc. Soc. Exper. Biol. & Med.* 38: 181, 1938.
- Smith, L. C.: Collapse with death following the use of amphetamine sulfate, *J.A.M.A.* 113: 1022, 1939.
- Tainter, M. L., L. J. Whitsell and J. M. Dille: The analeptic potency of sympathomimetic amines, *J. Pharmacol. & Exper. Therap.* 67: 56, 1939.

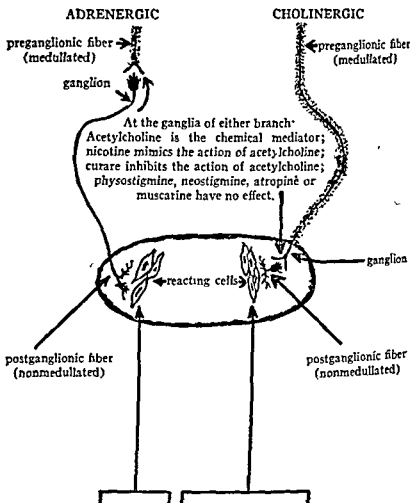
A number of drugs of wide clinical importance are classified as autonomic drugs because their action more or less resembles that produced by stimulation or inhibition of either sympathetic or parasympathetic nerves. The action of these drugs can be most readily interpreted in terms of the chemical-mediation theory of nerve transmission across a synapse. In brief, it is believed that impulses traveling along preganglionic fibers of both parasympathetic and sympathetic nerves cause the release of acetylcholine, which transmits the impulses across the synapse to the postganglionic fibers. Impulses traveling down the postganglionic fibers of most sympathetic nerves liberate sympathin, a substance similar if not identical with epinephrine (adrenaline), while those traveling down postganglionic fibers of parasympathetic nerves liberate acetylcholine. Acetylcholine, liberated either at the synapses or at the nerve endings, is normally rapidly destroyed by an enzyme, acetylcholinesterase (choline esterase), while sympathin is probably similarly destroyed by amine oxidase.

## INTRODUCTION

INTRODUCTION	SYNTHETIC
SYMPATHOMIMETIC DRUGS	SYMPATHOMIMETIC AMINES
EPINEPHRINE	SYMPATHOLYTIC DRUGS
EPHEDRINE	PREPARATIONS

# Autonomic Drugs

## SCHEMATIC ILLUSTRATION OF THE ACTION OF AUTONOMIC DRUGS



Sympathin (epinephrine?) is the chemical mediator.

Ephedrine potentiates by inhibition of amine oxidase.

Epinephrine acts directly on the sensitive area of the reacting cell.

Ergotamine may partially block the stimulant action in toxic doses.

*Acetylcholine is the chemical mediator.*

Physostigmine, neostigmine, potentiate by inhibition of choline esterase.

Acetylcholine, muscarine, act directly on the sensitive area of the reacting cell.

Atropine inhibits the response to all but direct stimulation of the reacting cell.

Acetylcholine is also liberated at the endings of certain postganglionic sympathetic nerve fibers (notably the nerves to the sweat glands and pilomotor muscles in human beings). Nerve endings at which acetylcholine is liberated are described as cholinergic, in distinction from those at which sympathin is liberated, which are said to be adrenergic. As a result of the action of acetylcholine at the ganglionic synapses of both branches of the autonomic nervous system as well as at the postganglionic nerve endings of all parasympathetic and certain sympathetic fibers, there are two distinct groups of responses to acetylcholine administration. The effects initiated at the ganglionic synapse are similar to those obtained with injections of nicotine and are described collectively as the nicotinic action of acetylcholine. The effects initiated at postganglionic cholinergic nerve endings are similar to those obtained by the injection of muscarine and are described collectively as the muscarinic action of acetylcholine. The nicotinic effects can be abolished by curare, the muscarinic by atropine.

The chemical-mediation theory of transmission of nerve impulses was expanded in 1936 by Dale and his co-workers, who demonstrated the presence of acetylcholine at the end plates of motor nerves to voluntary muscles. The action of acetylcholine at these end plates is nicotinic in nature, being abolished by curare. Recently, considerable attention has been paid to the possible role of acetylcholine in synaptic transmission in the central nervous system.

Drugs which when injected elicit responses stimulating those of stimulation of adrenergic nerve fibers are known as sympathomimetic drugs. Drugs which elicit responses stimulating inhibition of adrenergic nerve fibers are known as sympatholytic drugs. Similarly, drugs whose action stimulates the muscarinic effect of acetylcholine are described as parasympathomimetic drugs, while those which inhibit this effect are described as parasympatholytic drugs. It should be realized that because of the close interrelation-

ship of the two branches of the autonomic nervous system supplying any given organ, stimulation of one branch may lead to a compensatory stimulation of the other; thus variable and unpredictable effects may ensue. Likewise, inhibition of one branch may be tantamount to stimulation of the other, since the normal counteracting mechanism has been abolished. Furthermore, parasympathomimetic drugs may, especially in larger doses, have nicotinic actions which produce sympathomimetic as well as parasympathomimetic effects. Finally, in addition to their effects on the autonomic nervous system, autonomic drugs frequently have also a central effect which may at times overshadow their peripheral effects.

### SYMPATHOMIMETIC DRUGS

Sympathomimetic drugs can be classified pharmacologically as true sympathomimetic drugs which stimulate the effector mechanism directly and pseudosympathomimetics, which act by preserving sympathin, presumably by blocking the amine oxidase. The first group includes epinephrine, phenylephrine (neosynephrine), kephrine and cobefrine; the second, ephedrine, amphetamine, propadrine and paredrine.

#### EPINEPHRINE

Epinephrine (adrenaline) is the active principle of the adrenal medulla. It is prepared commercially either synthetically or from glands obtained from the slaughterhouse. The naturally obtained product is levorotatory; the dextrorotatory form has little physiologic activity. Optically inactive or racemic epinephrine is about one-half as active physiologically as levorotatory epinephrine.

**Actions.** The effect of epinephrine on any given organ is similar to that of stimulation of postganglionic adrenergic fibers supplying that organ and hence may be excitatory or inhibitory, depending on the organ, the species of animal and other factors, such as presence or absence of certain sex

hormones. Effects of therapeutic significance include contraction of arterioles, cardiac stimulation, dilation of the coronaries, relaxation of the bronchioles and dilation of the pupil. Other effects include contraction of the radial muscle of the iris, augmentation of salivary secretion, inhibition of the small intestine, excitation of the retractor penis, constriction of the spleen, inhibition of the nonpregnant and excitation of the pregnant human uterus.

**Administration.** Epinephrine is ineffective by mouth except in occasional hypersensitive patients. Solutions of epinephrine in isotonic solution of sodium chloride are marketed for use in nasal sprays. Recently, a suspension of epinephrine, containing 1 part epinephrine in 500 parts of vegetable oil, has been introduced with a view to prolonging the action of the drug by slowing absorption. Dilute aqueous solutions of epinephrine are quite unstable and commercial preparations frequently contain sodium bisulfite as a preservative.

**Toxicity.** Symptoms of overdosage with epinephrine include nausea, pallor, feeling of oppression and fear, throbbing headache, vertigo, tachycardia and hypertension. The use of too concentrated solutions may lead to local tissue necrosis, especially in sensitive individuals. Severe toxic manifestations include acute pulmonary edema, acute cardiac dilation and acute ventricular fibrillation. In persons with cardiovascular disease, and occasionally in apparently normal individuals, death or permanent mental impairment may result from a cerebral accident. Treatment is symptomatic, the symptoms usually passing off in a few hours. Epinephrine should be avoided in aged or hypertensive patients and in cases of heart disease. It is contraindicated in light chloroform or in cyclopropane anesthesia because of the danger of initiating ventricular fibrillation. Hypertensive patients have an increased sensitivity to epinephrine, especially as regards the cardiovascular response, and it should be avoided or used cautiously in such cases. This

increased response to epinephrine formed the basis of one of the earlier clinical tests for hyperthyroidism (Goetsch's test).

**Therapeutic Uses.** **CIRCULATORY EMERGENCIES.** Epinephrine increases the heart rate and the force of contraction and raises the blood pressure by peripheral vasoconstriction. It is thus of value in circulatory emergencies when a competent circulatory system becomes suddenly depressed, as in drowning accidents, carbon-monoxide poisoning, over-anesthesia, etc. Epinephrine is administered parenterally in doses up to 1 cc. of a 1:1000 solution. Administration is either subcutaneous, intramuscular, intravenous or intracardial, depending on the severity of the condition.

Epinephrine is of doubtful value in shock. It is believed that in shock the arterioles are already maximally contracted and such effect as epinephrine might have on the capillaries would not cause any great shift in the blood away from the abdominal regions and might have the disadvantage of increasing tissue hypoxia.

**Asthma.** Epinephrine dramatically relieves asthmatic paroxysms by relaxation of the smooth muscle of the bronchioles and by vasoconstriction of engorged bronchial mucosae. Its disadvantages, however, are its short action, its ineffectiveness orally, and its tendency to cause dryness and irritation of mucous membranes. A more prolonged effect can be obtained with intramuscular injection of oily suspensions. (Subcutaneous injection of such preparations may lead to local irritation or scar formation.) Inhalation of epinephrine in the form of a fine mist should be undertaken only under medical supervision because of the dangers of the strength of the solution used (1:100).

**Local Vasoconstriction.** Epinephrine is usually added to procaine and a number of other local anesthetics in order to delay absorption, thus increasing the duration and intensity of anesthesia as well as decreasing the systemic effects of the drug. Furthermore, the risk of hemorrhage is lessened

by the comparative bloodlessness of the field. In these preparations the concentration of epinephrine varies from 1:100,000 to 1:200,000.

Epinephrine in 1:1000 solution may be used to shrink the nasal mucosa in acute rhinitis but because of the brevity of its action and its tendency to produce "after-congestion" it is not the drug of choice in this condition. It is also used in the treatment of allergic responses, such as urticaria, angioneurotic edema, anaphylaxis, serum sickness, nitritoid reactions and hay fever. For these conditions up to 1 cc. of the 1:1000 solution may be injected subcutaneously.

Epinephrine sprayed on raw and bleeding surfaces may prevent excessive loss of blood by hemorrhage. However, the possibility of systemic toxicity from the large absorptive area should not be overlooked.

Introduction of epinephrine in the conjunctival sac is sometimes effective in the alleviation of glaucoma, the pupillary dilation and the constriction of the vascular bed reducing the ocular tension. However, in some cases, especially in acute glaucoma, there may be a dangerous rise of tension. Epinephrine finds further use in ophthalmology, often in conjunction with atropine, in breaking up adhesions of the iris to the lens by dilation of the pupil. Standardization of Epinephrine. A U.S.P. reference standard is available. The official method of assay is based upon the rise of blood pressure in the anesthetized dog. Chemical methods are available but are less sensitive and less specific.

### EPHEDRINE

The alkaloid ephedrine was first isolated in 1887 by the Japanese chemist, Nagai, from a Chinese shrub, Ma-huang (*Ephedra equisetina*). It is obtained commercially from various species of *Ephedra* or produced synthetically. The naturally isolated product is levorotatory. The synthetic ephedrine is usually racemic and is only about half as active



as the natural ephedrine since the dextrorotatory form is practically inert pharmacologically.

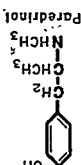
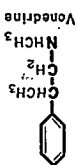
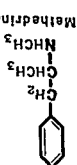
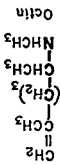
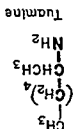
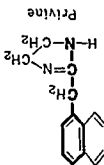
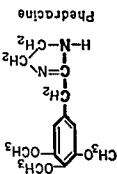
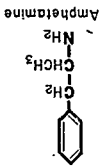
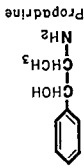
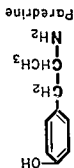
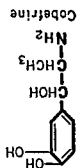
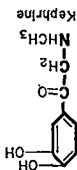
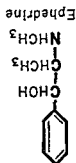
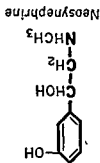
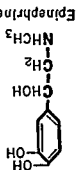
Ephedrine augments the effects of injected epinephrine or of sympathetic stimulation. It has been suggested that this effect is due to an inhibition of the destruction of sympathin by amine oxidase. Hence the sympathomimetic effect of ephedrine would be due to a prolongation of the life of sympathin continually liberated at the nerve endings.

Ephedrine has essentially the same uses as epinephrine. It has the advantages of being effective by mouth, more stable and longer acting. Its disadvantages include the slower onset of its effects, the lessened effect of repeated doses (tachyphylaxis) and its pronounced stimulatory effect on the central nervous system. Like epinephrine, ephedrine tends to have a marked effect on the heart and should be avoided in cardiovascular diseases. Ephedrine is of some value in the treatment of myasthenia gravis, its use in this condition predating that of neostigmine. While the mechanism of action in this condition is not wholly understood, recent work indicates that transmission of impulses along motor nerves is improved by ephedrine.

Toxic symptoms of overdosage or hypersensitivity are manifested by sympathetic stimulation as well as by central nervous system stimulation suggestive of a convulsant poison. Dysuria and urinary retention are at times noted, and in fact strangury may be an annoying feature in the clinical use of ephedrine and other sympathomimetics.

#### SYNTHETIC SYMPATHOMIMETIC AMINES

The numerous pharmacologic effects of ephedrine and epinephrine are a distinct disadvantage clinically when undesirable side-effects limit their usefulness. Efforts have been made, therefore, to synthesize related compounds which would be useful for a particular purpose and be relatively free from other effects. Such compounds are conveniently referred to as sympathomimetics, though in many instances



they retain little of the sympathomimetic patterns of epinephrine or ephedrine. Literally hundreds of such compounds have been prepared and a number of them have been adopted for clinical use. In order to evaluate these newer drugs, one should consider how they measure up to the qualifications for a particular use. Thus, a pressor drug used to maintain or restore the blood pressure during or after a surgical operation *should be effective by intravenous or intramuscular injection*; it should rapidly produce a sustained rise in blood pressure and should have no untoward effects on the cardiovascular system. Epinephrine gives a rapid and marked rise in blood pressure but its duration is short and it may be followed by a precipitous fall. Ephedrine has a somewhat more gradual and longer-lasting effect but it is not so effective on repeated injection and has undesirable stimulating effects on the central nervous system. Among the newer drugs, phenylephrine (neosynephrine), paredrine, phedracine, paradrinol (veritol, pholedrine) and the aliphatic amine oenethyl are said to have prolonged pressor effects with little cardiac or central nervous system stimulation, and are reported to be effective on repeated injection. Unfortunately, none of these drugs is effective for more than half an hour. Methedrine (d-desoxyephedrine) is claimed to have a much more lasting effect, though its cortical-stimulatory action may counteract postoperative sedation.

In selecting a drug for a nasal decongestant, a prolonged effect, without a period of after-congestion and freedom from central nervous system or cardiac stimulation are prime prerequisites. A volatile substance makes for ease of administration in the form of an inhalant. The drug should be able to penetrate mucus, should not interfere with the nasal cilia and should not produce any local irritation. Oily preparations are to be deprecated because of the interference with ciliary movements and because of the danger of lipoid pneumonia. Epinephrine causes too much after-con-

gestion and ephedrine too much central stimulation to be satisfactory nasal decongestants. Amphetamine (benzedrine), vonedrine, and the aliphatic amine, tuamine, are volatile bases dispensed as inhalants. Amphetamine has a pronounced central-stimulatory effect and gives rise to nervousness and insomnia unless used very sparingly. Naphazoline (privine) has a very intense and prolonged vasoconstrictor action which, however, may be followed by an annoying congestion, which limits its use. Phenylephrine and propadrine have a more prolonged action than ephedrine and appear to be relatively free from central-stimulatory effects but must be applied by sprays or as nose drops.

Drugs used to enhance or prolong the effect of local anesthetics include cocaine and phenylephrine, which possess the local vasoconstricting effect of epinephrine but are said to be less toxic and to cause fewer side-effects, such as central nervous system and cardiac stimulation. However, they are less efficient vasoconstrictors than epinephrine and higher concentrations are therefore required. Kephirine is a local vasoconstrictor, less powerful but more prolonged in action than epinephrine. It is used locally to control capillary bleeding.

The aliphatic amine, octin, has a spasmodic action, presumably due both to a direct action on smooth muscle and to a stimulation of inhibitory sympathetic fibers. It has been recommended for the relief of spasm of the intestinal, biliary and genitourinary tracts.

## SYMPATHOLYTIC DRUGS

Several drugs, such as ergot, yohimbine and certain dioxane derivatives have a depressant action on the sympathetic nervous system. These drugs are too toxic for routine clinical use, and, therefore, in combating overactivity of the sympathetic nervous system recourse has to be made either to sympathectomy or to parasympathetic stimulation. The need for a safe sympatholytic is apparent in view of the

various conditions whose basis may well be an autonomic imbalance, such as hypertension, Reynaud's disease, megacolon and certain nervous conditions.

In 1939 a study was made in Germany of the sympatholytic properties of a number of imidazoline derivatives. One of these compounds, 2-benzyl-4,5-imidazoline or priscol, has been used clinically in Europe, apparently with promising results. A similar but probably more potent compound, N, N-dibenzyl- $\beta$ -chloroethylamine or dibenamine, is being studied in this country with a view to determining its clinical value and its usefulness in physiologic and pharmacologic investigations.

### PREPARATIONS

Epinephrine U.S.P.; adrenaline B.P.

Epinephrine solution U.S.P. A 1:1000 solution of epinephrine hydrochloride in distilled water.

Solution of adrenaline hydrochloride B.P. A 1:1000 solution of adrenaline hydrochloride in physiologic saline.

Epinephrine injection U.S.P. *Sterile solution of epinephrine hydrochloride in water for injection. It is usually available as 1 cc. of 1:1000 solution; 10 cc. of 1:1000 solution; 30 cc. of 1:1000 solution. 1 mg.*

Epinephrine inhalation U.S.P. 1:100 solution of epinephrine in distilled water.

Suspension of epinephrine in oil, 1:500 N.N.R. A suspension of epinephrine U.S.P. in vegetable oil. 0.2-1.5 cc.

Ephedrine hydrochloride U.S.P.; B.P. Ephedrine sulfate U.S.P. 25 mg.

Ephedrine-sulfate tablets U.S.P.; B.P. Usually available in 15, 25, 30, and 45 mg. amounts.

Racephedrine N.N.R. Racemic ephedrine. 30-50 mg.

Racephedrine sulfate and hydrochloride N.N.R. 30-50 mg.

Phenylephrine hydrochloride N.N.R.

Amphetamine N.N.R.

Vonedrine N.N.R.

Tuamine N.N.R.  
 Tuamine sulfate N.N.R.  
 Naphazoline hydrochloride N.N.R.  
 Propadrine hydrochloride N.N.R.

## BIBLIOGRAPHY

### GENERAL

Burn, J. H.: The relation of adrenaline to acetylcholine in the nervous system, *Physiol. Rev.* 25: 377, 1945.  
 Loewi, O.: The humoral transmission of nervous impulse, *Harvey Lectures* 28: 218, 1932-1933.  
 Myerson, A.: Human autonomic pharmacology, XII, theories and results of autonomic drug administration, *J.A.M.A.* 110: 101, 1938.

### SYMPATHOMIMETIC DRUGS

Brunner, R. S., and G. de Takats: The use of neosyn-  
 ephrine in spinal anesthesia, *Surg. Gynec. & Obst.*  
 68: 1021, 1939.  
 Baumgardner, J. S., L. D. Abernethy and F. B. Zimmer-  
 man: Vonedrine; clinical study of a new nasal decon-  
 gestant, *Laryngoscope* 54: 408, 1941.  
 Butler, D. B., and A. C. Ivy: Method of application of  
 drugs to the nasal mucosa—a comparison of nasal  
 drops, sprays and inhalers, *Arch. Otolaryng.* 39: 109,  
 1944.  
 Cohen, A. E., and M. L. Waterstone: Epinephrine hyper-  
 sensitivity, *J. Allergy* 11: 393, 1939-1940.  
 Edgeworth, H.: A report of progress on the use of ephed-  
 rine in a case of myasthenia gravis, *J.A.M.A.* 94: 1136,  
 1930.  
 Elmes, P. C., and A. A. Jefferson: Action of pholedrine  
 and neosynephrin in raising the blood pressure, *Brit.*  
*M. J.* 2: 65, 1942.  
 Reinberg, S. M., and S. Friedlander: Nasal congestion  
 from frequent use of privity hydrochloride, *J.A.M.A.*  
 128: 1095, 1945.  
 Gunn, J. A.: The pharmacological actions and therapeu-  
 tic uses of some compounds related to adrenaline, *Brit.*  
*M. J.* 2: 155, 214, 1939.

- Hartung, W. H.: Inactivation and detoxication of pressor amines, *Ann. Rev. Biochem.* 15:593, 1946.
- Keeney, E. L., J. A. Pierce and L. N. Gay: Epinephrine in oil, a new, slowly absorbed epinephrine preparation, *Arch. Int. Med.* 63:119, 1939.
- Kully, B. M.: The use and abuse of nasal vasoconstrictor medications, *J.A.M.A.* 127:307, 1945.
- LeCompte, C. B.: Some clinical experiences with (o-ethyl) 2-methyl-amino-heptane as a vasopressor substance, *Anesth. & Analg.* 25:168, 1946.
- Sterling, A.: Dangers attending the clinical use of epinephrine in bronchial asthma, *M. Clin. North America* 24:1851, 1940.
- Sympathomimetic agents—A symposium, *Indust. & Engin. Chem.* 37:116, 1945.

#### SYMPATHOLYTIC DRUGS

- Chess, D., and F. F. Yonkman: Adrenolytic and sympatholytic actions of prisco (benzyl-imidazoline), *Proc. Soc. Exper. Biol. & Med.* 61:127, 1946.
- Nickerson, M., and L. S. Goodman: Pharmacological properties of a new adrenergic blocking agent: N, N-dibenzyl- $\beta$ -chloroethylamine (dibenamine), *J. Pharmacol. & Exper. Therap.* 89:167, 1947.

# Autonomic Drugs

## PARASYMPATHOMIMETIC

### DRUGS

#### CHOLINE DERIVATIVES

#### PHYSOSTIGMINE AND

#### NEOSTIGMINE

#### DI-ISOPROPYL FLUOROPHOS-

#### PHATE

#### Pilocarpine

#### Muscarine and

#### Arecoline

#### THERAPEUTIC USES OF PARA-

#### SYMPATHOMIMETIC

### DRUGS

## PARASYMPATHOLYTIC DRUGS

### BELLADONNA ALKALOIDS

### SYNTHETIC PARASYMPATHO-

### LYTIC DRUGS

### THERAPEUTIC USES OF PARA-

### SYMPATHOLYTIC DRUGS

### ATROPINE POISONING

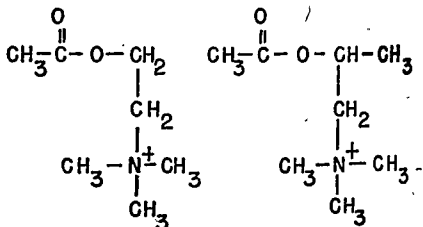
### PREPARATIONS

Parasympathomimetic drugs include the choline deriva-  
tives, such as acetylcholine, methacholine (mechoyl) and  
carbachol; physostigmine (eserine); neostigmine (prostig-  
mine) and pilocarpine. Clinically, these drugs are used to  
stimulate a depressed parasympathetic system or to antago-  
nize an overactive sympathetic nervous system and to im-  
prove the transmission of impulses at the myoneural  
junction of skeletal muscle. There is evidence that in some  
cases their therapeutic action may be due to an effect on  
the central nervous system.

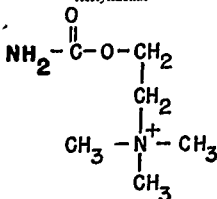
Acetylcholine was first studied pharmacologically in  
1906 by Hunt and Taveau, who were attempting to identify



## CHOLINE DERIVATIVES



Acetylcholine



Methacholine

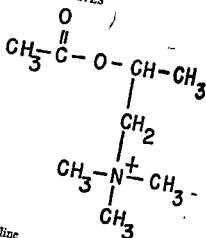
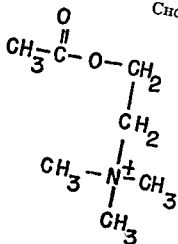
the substance responsible for the blood-pressure-lowering activity of the adrenal gland after the epinephrine had been extracted. They succeeded in isolating choline but in insufficient quantities to account for the observed effects. In the belief that the choline was the end product in the breakdown of a more active compound, these investigators tested acetylcholine and observed its very potent blood-pressure-lowering effect. Their suggestion that acetylcholine was present in the adrenal gland, however, was met with considerable scepticism. The compound was later studied by Dale, who

observed the remarkable similarity between the effects of acetylcholine and of stimulation of parasympathetic nerves and who first suggested that this drug might play the role of a parasympathetic hormone. The first direct evidence of such an action was presented in 1921 by Otto Loewi, who stimulated the vagus of an isolated frog heart and on perfusing a second heart with the Kinger's fluid from the stimulated heart obtained a slowing similar to that produced by stimulation of the vagus. However, no slowing was observed if the second heart was atropinized. Loewi suggested that the heart is not stimulated directly by the vagus but by a substance which he called *Vagusstoff*, which is liberated by vagus stimulation. The behavior of this substance was shown by Loewi and others to be similar to that of acetylcholine. In 1929 Dudley and Dale isolated acetylcholine from animal tissue (spleen). Later workers, using refined techniques of bioassay, have shown the presence of acetylcholine at nerve endings, ganglionic synapses and in the central nervous system, giving strength to the conception that acetylcholine plays an important role in the transmission of nerve impulses across the synapse and at the neuromuscular junction.

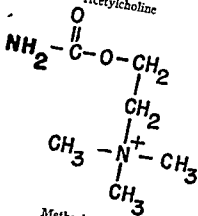
The well-established parasympathetic stimulatory action of acetylcholine is of no therapeutic value because of the instability of the drug and its evanescent action. A number of more stable choline derivatives, however, and wide clinical application.

Methacholine (mechoyl, acetyl- $\beta$ -methylcholine) was first studied pharmacologically in 1911 by Hunt and Taveau, who were endeavoring to find a drug which would give a more persistent blood-pressure-lowering effect than acetylcholine. The compound did not arouse any widespread clinical interest, however, until some twenty years later, following the work of Simonart. It is the drug of choice in the treatment of peripheral vascular disease, in which it gives symptomatic relief by improving the circulation. It is suf-

## CHOLINE DERIVATIVES



Acetylcholine

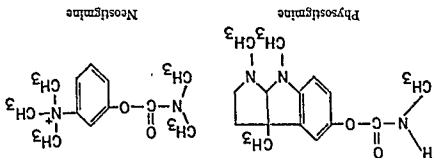


Methacholine

the substance responsible for the blood-pressure-lowering activity of the adrenal gland after the epinephrine had been extracted. They succeeded in isolating choline but in insufficient quantities to account for the observed effects. In the belief that the choline was the end product in the breakdown of a more active compound, these investigators tested acetylcholine and observed its very potent blood-pressure-lowering effect. Their suggestion that acetylcholine was present in the adrenal gland, however, was met with considerable scepticism. The compound was later studied by D.-

properties due to their greater penetrability. Such compounds have a mydriatic and cycloplegic action on the eye in contrast to the myotic and cyclotonic action associated with parasympathomimetic drugs. The action is apparently similar to that of atropine and is due to a paralysis of the parasympathetic system rather than a stimulation of the sympathetic. One such drug, the dibutyl carbamate of dimethyl ethyl- $\beta$ -hydroxyethyl ammonium sulfate (dibutyl line sulfate), has been tried clinically as a cycloplegic. It is claimed to be a rapidly acting drug giving a short period of visual disability with negligible systemic effects. Disadvantages include irritation with continued use and disturbance of the corneal epithelium due to the surface activity of the drug.

#### PHYSOSTIGMINE AND NEOSTIGMINE



Physostigmine (eserine) is obtained from the seed of *Physostigma venenosum*, the Calabar bean. Neostigmine (prostigmine) is a synthetic drug introduced in 1931 as a result of the work of Stedman and his associates. Both compounds owe their parasympathomimetic action to an inhibition of choline esterase and thus to a prolongation of the life of the acetylcholine at cholinergic nerve endings. A new series of parasympathomimetics, the fluorophosphates, were developed in the course of studies on toxic agents in warfare. Their activity and the duration of their effects is due to an irreversible inhibition of choline esterase.

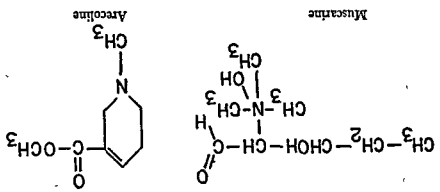
ficiently stable to be administered orally or subcutaneously, and it can be applied locally by iontophoresis. It has a very powerful effect on the heart and should not be given intravenously because of the danger of cardiac arrest. Unpleasant but less dangerous effects include the precipitation of asthmatic attacks in patients subject to asthma, dyspnea and substernal pain, epigastric discomfort, vomiting and disturbances in accommodation. These symptoms are common to all parasympathomimetics and can be promptly relieved by the injection of atropine. Methacholine has a much less pronounced nicotinic action than acetylcholine, though it is questionable whether the absence of a nicotine action is of great clinical significance since it would only be obtainable by undesirably large doses.

Carbachol (doryl, lentin, carbaminoylcholine), the most powerful choline derivative known, was synthesized in Germany in 1932. Under the name of lentin it became popular in that country for the treatment of gastro-intestinal disorders in animals. Because of its toxicity, it is seldom used except in the treatment of glaucoma when the eye does not respond to pilocarpine, physostigmine, methacholine or neostigmine. It is poorly absorbed from the conjunctival sac but absorption is improved when it is mixed with petrolatum or zephiran. It may cause blurring of vision and occasionally pain. It gives effective relief in the pain of peripheral vascular disease and by subcutaneous injection, its effects outlast those of methacholine. However, the latter is safer and it is to be preferred unless the patient is under constant medical supervision. Carbachol is said to have much less effect on the heart and blood vessels than methacholine. It has, however, a much more pronounced nicotine-like action.

**Choline Derivatives with Parasympatholytic Effects.** Swan (1943) prepared a series of choline derivatives having a surface-tension-lowering effect in the belief that such derivatives might have enhanced or altered pharmacologic

pathomimetic effect, the exact mechanism of which is not fully understood. Its action on sweat and salivary glands is especially marked.

MUSCARINE AND ARECOLINE



Muscarine is an alkaloid present in the mushroom, *Amanita muscaria*. It was first isolated and studied pharmacologically by Schmiedeberg in 1869. While at present of no clinical importance, it has had extensive use experimentally in the differentiation of smooth-muscle innervation since its action is at cholinergic nerve endings only and not, like acetylcholine, at both cholinergic nerve endings and at autonomic ganglia.

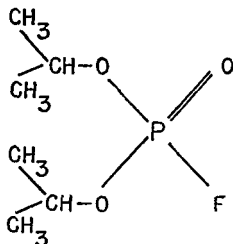
Arecoline is an alkaloid, obtained from the betel nut, which has a parasympathomimetic action. Its only use is in veterinary medicine in the treatment of gastro-intestinal disturbances.

Therapeutic Uses of Parasympathomimetic Drugs

I. Peripheral effects.

Local vasodilatation. The vasodilator effect of parasympathomimetic drugs has several clinical applications. The prevention or overcoming of vascular spasm gives symptomatic relief in peripheral vascular disease (e.g., Raynaud's disease, intermittent claudication, chronic ulcers, etc.).

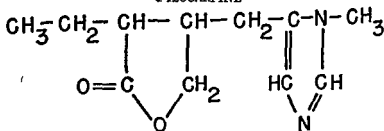
## DI-ISOPROPYL FLUOROPHOSPHATE



Di-isopropyl Fluorophosphate

in contrast to the reversible inhibition of physostigmine and neostigmine. Their effects last, therefore, until adequate amounts of choline esterase are built up again. Furthermore, their action, in therapeutic doses, is apparently nicotinic, rather than muscarinic. One of these drugs, *di-isopropyl fluorophosphate* (DFP), has had limited clinical use. It appears to be best suited for the treatment of glaucoma because of its long duration of action. It is too toxic to be of much value in the treatment of myasthenia gravis.

## PILOCARPINE



Pilocarpine

Pilocarpine is an alkaloid obtained from the leaves of the shrub *Pilocarpus jaborandi*. It has a specific parasymp-

preliminary studies indicate that di-isopropyl fluorophosphate offers the advantage of a prolonged action. Since the drugs are applied locally, the danger of systemic toxic effects is greatly reduced. Parasympathomimetic drugs, especially physostigmine, are also used to restore accommodation after the use of short-acting parasympatholytic drugs.

**STIMULATION OF THE GASTRO-INTESTINAL TRACT.** The parasympathomimetic drugs, especially methacholine, neostigmine and carbachol have been used in the relief and in the prevention of postoperative distention and urinary retention. The beneficial effects of the drugs are due to their stimulation of peristalsis by increasing the intestinal tone and their contraction of the bladder and relaxation of the trigone and sphincter.

## II. Conditions in Which Parasympathetic Stimulation is not Involved.

**MYASTHENIA GRAVIS.** Neostigmine is probably the best drug available for the symptomatic treatment of myasthenia gravis. This condition is believed to be due to a disturbance in the transmission of impulses at the myoneural junction of voluntary muscle. The dramatic improvement frequently afforded by neostigmine and also by physostigmine has been explained both by the inhibition of the choline esterase and by the antagonism of a hypothetical curare-like substance. Undesirable parasympathomimetic effects, such as salivation, perspiration, bradycardia and gastro-intestinal upsets, are abolished by the concomitant administration of atropine. Neostigmine can also be used as a diagnostic test for myasthenia gravis since in this disease a remarkable tolerance to the drug is developed, and the usual parasympathomimetic effects of neostigmine are elicited only by large doses.

**RELIEF OF MUSCLE SPASM.** Neostigmine has been recently reported to be of value in the relief of muscle spasms due to poliomyelitis, rheumatoid arthritis and allied conditions.



✓Methacholine has been used with good results in these conditions, either orally, subcutaneously or locally, by ion transfer. Carbachol is also effective but too toxic for routine use. Methacholine by iontophoresis has also been used in the treatment of arthritic pain and pelvic inflammation, relief being due to hyperemia, which may last from 4 to 8 hours. Recently, neostigmine has been used for the treatment of delayed menstruation. It is believed that the inhibition of the destruction of acetylcholine, effected by neostigmine, leads to the vasodilation and hyperemia of the uterus, which is thought to be one of the determining factors in the onset of the menstrual bleeding. If the patient is pregnant, bleeding rarely ensues, hence injection of neostigmine has been suggested as a test for early pregnancy but the possibility of inducing abortion limits its usefulness. Neostigmine has also been tried with promising results in the treatment of atrophic rhinitis. Application by nasal spray causes an increased blood flow to the nasal mucosa, with reduction in the encrustation and of the associated fetid odor.

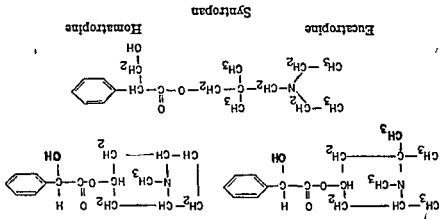
**SINUS TACHYCARDIA.** Stimulation of the vagus by parasympathomimetic drugs frequently brings about the arrest of attacks of sinus tachycardia when carotid pressure is ineffective. Neostigmine and methacholine are useful drugs in this connection. They do not, however, affect the heart rate if the tachycardia is associated with obvious organic disease.

**OPHTHALMOLOGY.** Parasympathomimetic drugs are important adjuncts in the treatment of glaucoma; the contraction of the ciliary body facilitates drainage through the canal of Schlemm, while vasodilation may also assist in the removal of fluid. Physostigmine is perhaps the most widely used drug for this purpose, though pilocarpine, neostigmine and methacholine are also effective. Carbachol (usually as a 0.75 per cent solution) has been used successfully in cases not responding to the usual treatment, while

The belladonna alkaloids have a depressant action on smooth muscles and glands innervated by postganglionic cholinergic nerve fibers. In larger doses they also have a depressant action on autonomic ganglia. The parasympatholytic effect is not due to a suppression of acetylcholine formation but to failure of the liberated acetylcholine to stimulate the atropinized cell.

The belladonna alkaloids, in addition to their characteristic peripheral effects, also have a central action; atropine and hyoscyamine at first stimulate and then depress the central nervous system, while the action of scopolamine is predominantly depressant.

### SYNTHETIC PARASYMPATHOLYTIC DRUGS



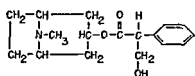
The manifold effects elicited by atropine stimulated the search for synthetic substitutes with a more specific action. Preparations used in ophthalmology include homatropine, eucatropine and E3 (dimethylaminoethyl benzilate ethochloride), which was recently introduced in England. These drugs act more promptly and have a much more evanescent effect on the eye than atropine. In addition, they are considerably less toxic and can be used on patients sensitive to atropine. Other compounds, such as homatropine methylbromide (novairine), syntropan and transeptin, are used

It has been suggested that relief is due to a central effect of the drug leading to inhibition of muscle tone in addition to the inhibition of choline esterase at the myoneural junction. As in the treatment of myasthenia gravis, undesirable parasympathomimetic effects are abolished with atropine.

## PARASYMPATHOLYTIC DRUGS

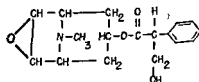
Depression of the parasympathetic nervous system is obtained clinically by the use of the belladonna alkaloids or by synthetic substitutes. In general, the synthetic substitutes do not display the variety of actions of the naturally occurring alkaloids. They do not, therefore, have as wide a field of application, but, on the other hand, their use in conditions for which they are effective is attended by fewer undesirable side effects.

### BELLADONNA ALKALOIDS



Atropine

(d, l, hyoscyamine)



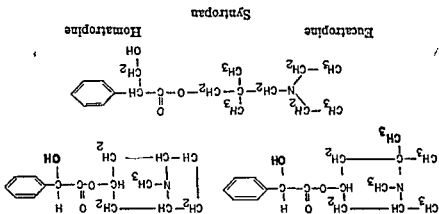
Scopolamine

The belladonna or solanaceous alkaloids, atropine, hyoscyamine and scopolamine (hyoscyne) are obtained from a number of solanaceous plants including *Atropa belladonna* (the deadly nightshade), *Datura stramonium* (Jimson weed) and *Hyocyamus niger* (henbane). Atropine rarely if ever occurs in nature and is formed by the racemization of the naturally occurring *l*-hyoscyamine. Since the pharmacologic activity is invested in the levorotatory form, atropine is approximately half as active as hyoscyamine. Scopolamine is the most active of the belladonna alkaloids, partly because of its greater solubility, which permits more rapid passage to the site of action.

The belladonna alkaloids have a depressant action on smooth muscles and glands innervated by postganglionic cholinergic nerve fibers. In larger doses they also have a depressant action on autonomic ganglia. The parasympatholytic effect is not due to a suppression of acetylcholine formation but to failure of the liberated acetylcholine to stimulate the atropinized cell.

The belladonna alkaloids, in addition to their characteristic peripheral effects, also have a central action; atropine and hyoscyamine at first stimulate and then depress the central nervous system, while the action of scopolamine is predominantly depressant.

# SYNTHETIC PARASYMPATHOLYTIC DRUGS



The manifold effects elicited by atropine stimulated the search for synthetic substitutes with a more specific action. Preparations used in ophthalmology include homatropine, eucatropine and E3 (dimethylaminoethyl benzoate ethochloride), which was recently introduced in England. These drugs act more promptly and have a much more evanescent effect on the eye than atropine. In addition, they are considerably less toxic and can be used on patients sensitive to atropine. Other compounds, such as homatropine methylbromide (novatrine), syntropan and transentan, are used

as antispasmodics, their effectiveness being due apparently both to a parasympathetic-depressant action and to a direct action on the muscle. These drugs have less effect than atropine on the eye, the salivary secretion and the heart rate. Isonipecaine, which is related chemically to atropine, is used chiefly for its morphine-like action. (See Chapter 9.)

## THERAPEUTIC USES OF PARASYMPATHOLYTIC DRUGS

### I. Peripheral Actions

**OPHTHALMOLOGY.** Parasympatholytic drugs cause a relaxation of the circular constrictor muscle (mydriasis) and of the ciliary body (cycloplegia). With atropine the effects may last for days and are not readily antagonized by physostigmine; hence, for routine eye examinations shorter-acting drugs such as homatropine and eucatropine are usually preferred. Atropine is of advantage when prolonged rest is indicated, as in some inflammatory conditions. It should not be used, however, if glaucoma is present or suspected since the relaxation of the ciliary body may impede drainage of the ocular fluid by blocking the canal of Schlemm.

**RELIEF OF SMOOTH-MUSCLE SPASM.** Atropine and a number of synthetic substitutes are useful in the treatment of gastro-intestinal spasm, especially in cases in which the underlying cause is thought to be overactivity of the parasympathetic nervous system. Atropine is included in many proprietary cathartics, allegedly to prevent griping. It is also used occasionally for the relief of biliary and urinary colic. Atropine is one of the most effective drugs in the treatment of enuresis in children, since it decreases the irritability and increases the capacity of the bladder.

The belladonna alkaloids were among the first remedies for bronchial asthma, inhalation of smoke from burning Jimson weed being a popular and fairly effective remedy. While atropine relaxes bronchial spasms and reduces se-

cretions, large doses are required, with attendant undesirable side effects; consequently the use of sympathomimetics is now preferred.

**HEART BLOCK.** Atropine occasionally restores the normal sinus rhythm in transient or intermittent heart block, presumably by its inhibitory action on the vagus.

**ARREST OF SECRETIONS.** Atropine is usually administered preoperatively to reduce bronchial and salivary secretions during anesthesia, though some operators claim that the resultant thick viscous mucus is as likely to cause complications as the more readily removed watery secretion which occurs without premedication.

## II. Central Actions

Scopolamine (0.3-0.6 mg. intramuscularly) relieves the rigidity and tremor of postencephalitic Parkinson's disease. The action is thought to be a central one since the efficacy of the atropine-like compounds in this disease is related to their central-depressant action.

Scopolamine (0.6 mg.) combined with morphine (8 mg.) has been used widely since its introduction as an obstetric analgesic by von Steinbüchel in 1902. A condition of amnesia and anesthesia results ("twilight sleep"), the patient remains more or less conscious but does not recall later the unpleasant circumstances of the event. This procedure has now fallen into disfavor in many clinics because of unfavorable influences on uterine contractions, the danger of markedly depressing the respiration of the child, and the fact that the relief of pain is often inadequate.

Atropine or scopolamine is frequently administered with morphine to counteract the respiratory depression of morphine. Scopolamine appears to be the drug of choice since it produces greater psychic depression and respiratory stimulation than atropine in equivalent dosage. The optimum ratio is 1 part of scopolamine (or atropine) to 25 parts of morphine.

Scopolamine, taken orally, is an effective prophylactic for seasickness and airsickness, probably because of both its central-depressant and its antispasmodic actions.

### ATROPINE POISONING

Atropine poisoning occurs frequently in children from the ingestion of belladonna plants or atropine-containing medicines. It may also occur accidentally during treatment; for example, sufficient atropine may occasionally be absorbed from the conjunctiva to give rise to systemic toxic effects. Both peripheral and central effects are apparent. The pupils become widely dilated. The skin is hot, dry and flushed and the temperature rises because of the inhibition of sweat secretion and the motor restlessness. Excitement may be marked and mental derangement may occur, followed by depression and collapse. Gastric lavage should be instituted if the poison was taken by mouth; barbiturates may be given to control the convulsions, while the peripheral symptoms may be treated with pilocarpine in 10 mg. doses subcutaneously, repeated until the mouth becomes moist. If depression has set in, stimulants and artificial respiration may be necessary.

### PREPARATIONS

Methacholine chloride U.S.P. 0.2 Gm. oral, 10 mg. subcutaneous.

Methacholine-chloride capsules U.S.P. Contains 0.2 Gm.

Methacholine-chloride injection. Contains 10 mg. in 1 cc.

Physostigmine salicylate U.S.P. and B.P. 2 mg.

Neostigmine bromide U.S.P. 15 mg.

Neostigmine methylsulfate U.S.P. 0.5 mg. subcutaneous or intramuscular.

Neostigmine-methylsulfate injection U.S.P. Usually available as 0.25 and 0.5 mg. per cc.

Pilocarpine nitrate U.S.P. and B.P. 5 mg.

Carbachol U.S.P.; B.P. (Carbaminoyl choline chloride) 2 mg. oral; 0.25 mg. subcutaneous.

- Carbachol injection U.S.P. 0.25 mg. in 1 cc.
- Carbachol tablets U.S.P. Usually 2 mg. tablets.
- Belladonna extract U.S.P.; B.P. 15 mg.
- Belladonna tincture U.S.P.; B.P. Approximately 0.03% alcoholic solution of the alkaloids of belladonna leaf.
- Liquid extract of belladonna B.P. Contains 0.75% alkaloids.
- Atropine U.S.P.; B.P. 0.4 mg.
- Atropine sulfate U.S.P.; B.P. 0.5 mg.
- Atropine-sulfate tablets U.S.P. Usually 0.3, 0.4, 0.5, 0.6 and 1.2 mg.
- Scopolamine (hyoscyne) hydrobromide U.S.P.; B.P. 0.5 mg.
- Scopolamine stable N.N.R. An aqueous solution of pure scopolamine protected against decomposition by the addition of 10% of mannite.
- Hyoscyamus U.S.P.; B.P. Dried leaf, with or without the tops, of *Hyoscyamus niger* Linné. 0.2 Gm.
- Hyoscyamus tincture U.S.P.; B.P. Approximately 0.004% (0.005% B.P.) alcoholic solution of alkaloids of hyoscyamus. 2-4 cc.
- Dry extract of hyoscyamus B.P. Contains 0.3% of alkaloids of hyoscyamus. 16-60 mg.
- Liquid extract of hyoscyamus B.P. Contains approximately 0.05% alkaloids of hyoscyamus.
- Eucatropine hydrochloride U.S.P. Used in ophthalmology as a 5% solution.
- Homatropine hydrobromide U.S.P.; B.P. Homatropine hydrochloride N.N.R. Used in ophthalmology as 1% solutions.
- Homatropine methylbromide N.N.R. 2.5 mg.
- Syntropan N.N.R. 50 mg.

## BIBLIOGRAPHY

## PARASYMPATHOMIMETICS

Alles, G. A.: The physiological significance of choline derivatives, *Physiol. Rev.* 14:276, 1934.



- Fox, M. J., and W. H. Spankus: The value of neostigmine in acute anterior poliomyelitis, *J.A.M.A.* 128: 720, 1945.
- Henderson, V. E. and M. H. Roepke: Drugs affecting parasympathetic nerves, *Physiol. Rev.* 17:373, 1937.
- Leopold, I. H. and J. H. Comroe, Jr.: Use of diisopropyl fluorophosphate ("DFP") in treatment of glaucoma, *Arch. Ophthalm.* 36:1, 1946.
- Moll, H. H.: The action of parasympathetic-mimetic drugs in asthma, *Quart. J. Med.* 33:229, 1940.
- O'Brien, C. S. and K. C. Swan: Carbaminoylecholine chloride in the treatment of glaucoma, *Simplex. Arch. Ophth.* 27:253, 1942.
- Simonart, A.: On the action of certain derivatives of choline, *J. Pharmacol. & Exper. Therap.* 46:157, 1932.
- Soskin, S., H. Wachtel and O. Hechter: Prostigmine methyl-sulfate for delayed menstruation; a therapeutic test for early pregnancy, *J.A.M.A.* 114:2090, 1940.
- Swan, K. C. and N. G. White: Choline esters with atropine-like action, *J. Pharmacol. & Exper. Therap.* 80: 285, 1944.
- Tractenberg, I. and W. Oliver: The use of prostigmin in abdominal and vaginal operations for the relief of postoperative distention and urinary retention in a series of 96 consecutive cases, *Am. J. Surg.* 53:284, 1941.
- Viets, H. R.: Myasthenia gravis, *J.A.M.A.* 127:1089, 1945.
- Waldman, S. and S. N. Moskowitz: The treatment of attacks of sinus tachycardia with prostigmin, *Ann. Int. Med.* 20:793, 1944.
- White, A. C. and E. Stedman: On the physostigmine-like action of certain synthetic urethanes, *J. Pharmacol. & Exper. Therap.* 41:259, 1931.
- Winkelstein, L. B.: Prostigmine methylsulfate and delayed menstruation, *Am. J. Obst. & Gynec.* 44:231, 1942.

#### PARASYMPATHOLYTICS

- Graham, D.P.D. and J. A. Gunn: The comparative activities of atropine, 1-hyoscyamine, hyoscyne and homatropine on mammalian smooth muscle, *Quart. J. Pharm. & Pharmacol.* 17:88, 1944.

- Henderson, V. E. and M. O. Sweeten: The effect of atropine on the gastro-intestinal canal and its glands. *Am. J. Digest. Dis.* 10: 241, 1943.
- Loman, J., P. G. Myerson and A. Myerson: Experimental pharmacology of post-encephalitic Parkinson's disease, *Arch. Neurol. & Psychiat.* 47: 399, 1942.
- Martin, J. E.: Atropine glaucoma, *Brit. M. J.* 1: 631, 1943.
- Morton, H. G.: Atropine intoxication, its manifestations in infants and children, *J. Pediat.* 14: 755, 1939.
- Phelps, M. L.: The role of the alkaloids of the belladonna plants in clinical anesthesia, *Anesthesiology* 3: 71, 1942.
- Wangeman, C. P. and M. H. Hawk: The effects of morphine, atropine and scopolamine on human subjects, *Anesthesiology* 3: 24, 1942.

# Histamine and Anti-histamine Drugs

INTRODUCTION

HISTAMINE

ANTERGAN AND NEOANTERGAN

DIPHENHYDRAMINE AND

TRIPLENNAMINE

PREPARATIONS

## INTRODUCTION

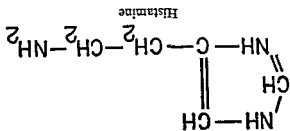
The probable role of histamine in inducing many of the symptoms of anaphylactic shock and other allergic disorders has prompted the search for preparations antagonistic to histamine. The antihistaminic agents discussed in this chapter are a newly introduced series of drugs which apparently interfere with the activity of histamine, possibly because of a competitive action with histamine at its site of action. Their action is not comparable, therefore, with that of pharmacologic antagonists to histamine such as epinephrine and certain antispasmodics.

The antihistamine drugs are such recent additions to therapeutics that their usefulness and their limitations cannot as yet be adequately appraised. However, the great demand for simple and effective relief from allergic disorders has already evoked widespread interest in the available compounds and will undoubtedly lead to the introduction of newer and possibly more effective agents.

## HISTAMINE

Histamine was first prepared synthetically by Windaus and Vogt in 1907 from iminazolypropionic acid. In 1910,

it was isolated from ergot simultaneously by Barger and Dale and by Kutscher and in the same year Ackermann prepared synthetic histamine by the action of putrefactive organisms on the amino acid histidine. This reaction is responsible for the formation of histamine in the gastrointestinal tract but probably little or none of the so-formed histamine is absorbed.

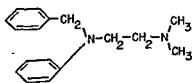


The pharmacodynamic and toxicologic actions of histamine vary considerably among the different species of animals. In the human being the main effects of histamine injection include stimulation of the bronchial, intestinal, venous and arterial smooth muscles, dilation of the arterioles and capillaries accompanied by an increased capillary permeability and a fall in blood pressure, and stimulation of the salivary, gastric and pancreatic glands. The similarity between these effects and the characteristic reactions of anaphylaxis was first observed by Dale and Laidlaw in 1910, while in 1926 Lewis and Grant suggested that the vascular reactions in the skin following various injuries and urticarial reactions were due to the liberation of histamine or a histamine-like substance ("H" substance) since they resembled so closely the effects of subcutaneously injected histamine. The possibility that histamine plays a role in the animal economy was further strengthened by the isolation of histamine from various tissues of the body by Abbel and Kubota in 1919 and Best, Dale, Dudley and Thorpe in 1927, and by various subsequent investigators. The belief that histamine plays a role in allergic disorders has led to various attempts to neutralize the his-

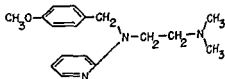
tamine as a therapeutic measure. On the assumption that patients suffering from allergies are hypersensitive to histamine, small doses of histamine have been administered with a view to effecting desensitization. The results have been inconclusive, however, leading to the suggestion that negative results were due to the nonantigenicity of histamine. Hence, attempts have been made to produce histamine antigens by conjugating histamine and various proteins, in particular, despeciated horse-serum globulin (histamine-azoprotein). Antibodies have apparently been produced in animals by this means but clinical results have not been encouraging. Histaminase, an enzyme capable of destroying histamine in vitro, appears to have no effect in vivo although at one time it was widely advocated as a treatment for allergic disorders. With the recent introduction of substances which apparently act by interference with histamine at its site of action, a new approach to the treatment of allergic disorders has been presented. It should be remembered, however, that the effect of these drugs is transient and symptomatic relief only is secured. Furthermore, the effect of these drugs on the development of immunity has not been determined.

Histamine is employed clinically in the histamine test of gastric function. This test is based on the fact that while histamine normally stimulates the acid-secreting cells, it is ineffective in promoting acid secretion in certain types of achlorhydria, especially that associated with pernicious anemia.

### ANTERGAN AND NEOANTERGAN



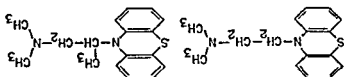
Antergan  
(2339RP)



Neoantergan  
(2786RP)

A systematic search for substances antagonistic to histamine was first undertaken in 1937 by Bovet and Staub, working in Fournau's laboratory in France. These investigators first studied a number of sympatholytic and antispasmodic drugs which had been shown earlier by Fournau and other workers to inhibit some of the actions of histamine. Various phenolic ethers and ethylenediamine preparations were studied but found to be too toxic for therapeutic use. However, in 1942 Halpern prepared a series of ethylenediamine compounds closely related to those studied by Bovet and Staub. One of these compounds, dimethylaminoethylbenzylamine (antergan or 2339RP) has been used therapeutically in Europe for the relief of various allergic disorders, apparently with promising results. Subsequently, Bovet and his associates introduced another ethylenediamine derivative N-p-methoxybenzyl-N-dimethylaminomethylaminopyrine (neoantergan or 2786RP), which they claim is better tolerated than antergan. These compounds have had little clinical use in America so that a comparison cannot be drawn between them and the antihistaminic substances developed in this country.

Recently, Halpern has reported the development of two new compounds, 3015 and 3277, which are much more effective antihistamine agents than antergan or neoantergan.

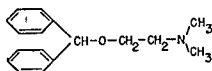


3015

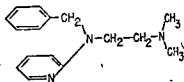
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Preliminary therapeutic trials indicate that these drugs cause some drowsiness but no symptoms of digestive intolerance.

## DIPHENHYDRAMINE AND TRIPELENNAMINE



Diphenhydramine Hydrochloride  
(Benadryl)



Tripeleennamine Hydrochloride  
(Pyribenzamine)

Diphenhydramine hydrochloride (benadryl,  $\beta$ -dimethylaminoethylbenzhydryl ether hydrochloride) was introduced in 1945 by Loew and his associates after a study of the antihistamine activity of a number of benzhydryl alkamine ethers. The experimental criteria of activity was reduction of bronchial constriction in guinea pigs that had been exposed to atomized histamine solutions. Other antihistaminic effects observed include antagonization of the bronchoconstriction in sensitized guinea pigs subjected to anaphylactic shock and suppression of the fall of blood pressure following small doses of histamine in anesthetized dogs. Diphenhydramine also possesses musculotropic and neurotropic activity since it antagonizes the spasmogenic effects of barium and of acetylcholine on the guinea-pig intestine, though in doses larger than those required to abolish the spasmogenic action of histamine.

Diphenhydramine has given promising results in the treatment of urticaria, angioneurotic edema, seasonal allergic rhinitis, serum reactions and drug sensitivities. It has proved of less value, however, in the treatment of asthma and nonseasonal allergic rhinitis. Its chief drawback is that it produces a state of drowsiness in many patients, which may lead to confusion and loss of judgment, though occasional cases of excitement and delirium after its use have been reported. Other toxic symptoms include gastrointestinal upsets, dryness of the mouth and hot flushes.

Tripeleennamine hydrochloride (N'pyridyl-N'benzyl-N-dimethylethylenediamine hydrochloride, pyribenzamine) was

introduced by Mayer and his associates in 1945 after a survey of the antihistamine activity of a series of pyridine derivatives. Its pharmacologic and therapeutic properties are essentially similar to those of diphenhydramine, though it is said to cause fewer toxic reactions and is apparently more effective in both seasonal and nonseasonal allergic rhinitis. It has also been used locally in the form of a 2 per cent ointment for the relief of itching of allergic origin.

## PREPARATIONS

Histamine phosphate U.S.P.; B.P. 0.3 mg. intramuscular. Histamine-phosphate injection U.S.P. Contains 1 Gm. in 1000 cc.

Diphenhydramine hydrochloride (benadryl) N.N.R. 50 mg. Tripeleannamine hydrochloride (pyribenzamine) N.N.R. 50 mg.

## REFERENCES

### GENERAL

Feinberg, S. M.: Histamine and antihistaminic agents, their experimental and therapeutic status, J.A.M.A. 132:702, 1946.

### HISTAMINE

Abel, J. J., and S. Kubota: On the presence of histamine ( $\beta$ -iminazolyethylamine) in the hypophysis cerebri and other tissues of the body and its occurrence among the hydrolytic decomposition products of proteins, J. Pharmacol. & Exper. Therap. 13:243, 1919.  
 Best, C. H., and E. W. McHenry: Histamine, Physiol. Rev. 11:371, 1931.  
 Best, C. H., H. H. Dale, H. W. Dudley and W. V. Thorpe: The nature of the vaso-dilator constituents of certain tissue extracts, J. Physiol. 62:397, 1927.  
 Dale, H. H., and P. R. Laidlaw: The physiological action of  $\beta$ -iminazolyethylamine, J. Physiol. 41:318, 1910-1911.  
 Dragstedt, C. A.: The significance of histamine in anaphylaxis, J. Allergy 16:69, 1945.  
 Dundy, H. D., B. Zohn and R. Chobot: Histamine azo-protein: clinical evaluation, J. Allergy 18:1, 1947.



- Fell, N., G. Rodney and D. E. Marshall: Histamine-protein complexes: synthesis and immunologic investigation, 1. Histamine-azoprotein, *J. Immun.* 47:237, 1943.
- Lewis, T., and R. T. Grant: Vascular reactions of the skin to injury, part VII, notes on the anaphylactic skin reaction, *Heart* 13:219, 1926.

#### ANTERGAN AND NEOANTERGAN

- Dews, P. B., and J. D. P. Graham: The antihistamine substance 2786RP, *Brit. J. Pharmacol.* 1:278, 1946.
- Halpern, B. N.: Les antihistaminiques de synthèse, essais de chimiothérapie des états allergiques, *Arch. Int. Pharmacodyn.* 68:339, 1942.

#### DIPHENHYDRAMINE AND TRIPELENNAMINE

- Arbesman, G. E., G. F. Koepf and A. R. Lenzner: Clinical studies with n'pyridyl, n'benzyl, dimethyl ethylene diamine monohydrochloride (pyribenzamine), *J. Allergy* 17:275, 1946.
- Feinberg, S. M., and T. B. Bernstein: Tripeleennamine "pyribenzamine" ointment for the relief of itching, *J.A.M.A.* 134:874, 1947.
- Friedlaender, A. S.: The use of a histamine antagonist, beta-dimethylaminethyl benzhydryl ether hydrochloride, in allergic disease, *Am. J. M. Sc.* 212:185, 1946.
- Loew, E. R., M. E. Kaiser and V. Moore: Synthetic benzhydryl alkamine ethers effective in preventing fatal experimental asthma in guinea pigs exposed to atomized histamine, *J. Pharmacol. & Exper. Therap.* 83:120, 1945.
- Mayer, R. L.: Antihistaminic substances with special reference to pyribenzamine, *J. Allergy* 17:153, 1946.
- O'Leary, P. A., and E. M. Farber: Evaluation of beta-dimethylaminethyl benzhydryl ether hydrochloride (benadryl) in the treatment of urticaria, scleroderma and allied disturbances, *Staff Meetings Mayo Clinic* 21:295-297, 1946.
- Wells, J. A., H. C. Morris, H. B. Bull and C. A. Dragstedt: Observations on the nature of the antagonism of histamine by  $\beta$ -dimethylaminethyl benzhydryl ether (benadryl), *J. Pharmacol. & Exper. Therap.* 85:122, 1945.

Digitalis and related preparations are the most widely used drugs in diseases or disorders of the heart. The digitalis

## DIGITALIS AND RELATED PREPARATIONS

The heart drugs include substances acting directly on the heart, such as the digitalis group, quinidine and probably the xanthine derivatives; and substances acting on the coronary vessels, such as the nitrites, nitrates and papaverine. In a broader sense, the term also includes preparations which act mainly on the peripheral vascular system, such as the sympathomimetic amines (chap. 11) and posterior pituitary (chap. 21), which are used to maintain or elevate the blood pressure; parasympathomimetic drugs (chap. 12), which slow the heart by vagal stimulation and which are therefore of value in the treatment of paroxysmal tachycardia; diuretic drugs (chap. 15), which relieve the heart by ridding the body of excess fluid; morphine and isonipercaine (chap. 9), which relieve the pain and dyspnea of severe heart disease; oxygen (chap. 5), which relieves the hypoxia of congestive heart failure; and drugs used in the treatment of essential hypertension, which are included in the present chapter.

## INTRODUCTION

INTRODUCTION	DIGITALIS AND RELATED PREPARATIONS	QUINIDINE	XANTHINE DERIVATIVES	PREPARATIONS
NITRITES AND ORGANIC NITRATES	PAPAVERINE	DRUG THERAPY OF HYPERTENSION	PREPARATIONS	

## Heart Drugs

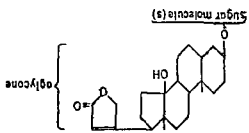
or foxglove plant was known to the herbalists in the sixteenth century, who used it as an external remedy. Its rational medicinal use was not developed until 1785, when William Withering, an English physician, published the results of 10 years' observations on the use of foxglove as a diuretic in dropsy. His investigations were prompted by the acquisition of a secret cure from an old woman in Shropshire. Although this remedy was composed of twenty ingredients, Withering soon found the therapeutically effective substance to be digitalis. Actually he considered its efficacy lay in its diuretic effect, although he did observe the effects of the drug on the heart. A few years later, however, the primacy of cardiac action of digitalis was recognized by both Cullen and Ferriar. The introduction of digitalis proved to be a revolutionary development since previously only comparatively ineffective drugs such as camphor and valerian were available for cardiac patients.

**Chemistry of the Cardiac Glycosides.** The cardiac action of digitalis is due to glycosides, which are conjugation products of sugars and nonsugars. The nonsugar moieties are known as aglycones or genins. A similar pharmacologic activity is found in a number of other plants in which the active agents are either glycosides or alkaloids, and in the venom of toads. The latter generally contains two classes of digitalis-like principles, the bufagins, which resemble aglycones, and the bufotoxins, which are conjugation products of bufagins and suberyl-arginine.

Glycosides, bufagins and bufotoxins all contain the steroid nucleus in common with cholesterol, the sex hormones, adrenal-cortical hormones and the vitamins D. The cardiac activity is associated with the unsaturated butyro-lactone ring attached to C<sub>17</sub>. The carbohydrate portion of the glycoside has no cardiac action itself but greatly increases the activity of the aglycone.

GENERAL STRUCTURE OF THE CARDIAC GLYCOSIDES

While cardiac glycosides are widespread in nature, the official sources of therapeutic preparations are limited to two species of digitalis (*D. purpurea* and *D. lanata*), two species of strophanthus (*S. kombé* and *S. gratus*), and *Urginea maritima* or squill. It is of interest to note that plants containing cardiac glycosides have long been used in the preparation of arrow poisons. These include *Strophanthus kombé* and *S. gratus*, *Thevetia nerifolia* and *Antiaris toxicaria* (upas tree).



A number of cardiac glycosides have been isolated and identified chemically. These do not necessarily represent the glycosides as they exist in the living plant or animal but are more probably derived from the native glycosides by the loss of one or more sugar molecules. Digitoxin, gitoxin and gitalin have been isolated from *Digitalis purpurea*. On complete hydrolysis they yield the aglycones digitoxigenin, gitoxigenin and gitalignin. Three glycosides have been isolated from *D. lanata*, lanatoside-A, lanatoside-B and lanatoside-C, which on partial hydrolysis yield digitoxin, gitoxin and digoxin, respectively. The various species of Strophanthus yield strophanthins, which are related but not identical; they are usually designated by the initial of the specific name of the species from which they are obtained, thus, K-strophanthin is obtained from *S. kombé* and G-strophanthin or ouabain from *S. gratus*. *Urginea maritima* yields a crystalline fraction scillaren-A and an amorphous fraction, scillaren-B, which is probably a mixture of two or more glycosides. A variety of squill, the

red squill, is used widely as an ingredient of rat poisons. In addition to the scillarens, it contains a substance highly poisonous to rats.

The use of galenical preparations of cardiac glycosides is being rapidly superseded by the use of the crystalline glycosides or of highly purified preparations. These have the advantage of stability, injectability and more accurate dosage. They are generally more rapidly absorbed when given orally and cause less gastro-intestinal irritation, in part because of the absence of nonabsorbable glycosides and of the much smaller doses required.

**Pharmacologic Actions.** All the cardiac glycosides produce essentially similar pharmacologic effects. Marked differences in rates of absorption and in dissipation of the glycosides account for the quantitative differences in their action. Following the administration of these drugs, the force of systolic contraction is increased, the diastolic size of the heart is reduced, the cardiac output increased and the venous pressure reduced. The heart rate is usually slowed, in part because of vagal stimulation, but the degree of slowing is usually not significant in cases of normal sinus rhythm. The conduction time is slowed, the P-R interval being prolonged. The mechanism of action underlying these effects is not wholly understood. While many investigators believe that the primary action is directly on the heart muscle, it has also been suggested that the cardiac changes are secondary to changes in the peripheral circulation, namely, a relief of venous engorgement by a redistribution of the blood. The diuretic action of digitalis is secondary to an improvement in circulation. Digitalis is of no value as a diuretic in the absence of heart disease.

**Therapeutic Uses.** Digitalis and related preparations are of particular value in the treatment of congestive heart failure. The pulse rate is decreased while the cardiac output is increased. The edema is relieved by diuresis, and dyspnea and cyanosis disappear as the circulation improves. The

cardiac glycosides are also of value in the treatment of auricular fibrillation and flutter. In the former, beneficial effects are achieved by the depressant action on the ventricular rate and conduction, which prevents the development of congestive failure and produces conditions favorable to the return of a normal auricular rhythm. In cases of auricular flutter, normal rhythm may be restored by a prolongation of the refractory period. In some cases, the flutter may be converted to fibrillation, with a slowed ventricular rate.

**Administration.** Preparations of digitalis and squills are generally administered orally. A number of purified digitalis preparations are suitable for intravenous or intramuscular injection but parenteral administration is only justified in cases of emergency. The *Strophanthus* glycosides are poorly absorbed from the gastro-intestinal tract. Their use is usually restricted to intravenous therapy, especially in patients who tolerate digitalis poorly.

The full effects of cardiac glycosides develop slowly even after intravenous injection. The glycosides are taken up rapidly by all tissues of the body and are excreted very slowly. Because of the slow excretion, repeated doses tend to lead to a cumulation of the active principles in the body and to the development of toxic symptoms. Hence, for clinical purposes, an adequate concentration is built up in the body with an initial series of large doses, or, rarely, a single, massive oral or intravenous dose, a procedure known as digitalization. When the desired therapeutic effects have been attained, the patient is put on a maintenance dose, which is actually dependent on the amount metabolized per day but which is determined clinically by the amount necessary to secure therapeutic effects without toxic symptoms. Thus the maintenance dose of powdered digitalis may vary between 0.2 Gm. per week and 0.2 Gm. per day. Toxicity. Symptoms of overdigitalization include loss of appetite, nausea, vomiting and occasionally diarrhea, visual

disturbances, including colored vision, double vision or temporary blindness, and headache. The pulse is usually markedly slowed. There may be paroxysmal tachycardia with complete or partial heart block, extrasystoles or ventricular fibrillation, which is the probable cause of death in fatal poisoning. In the normal individual, digitalis causes a decrease in cardiac output and an impairment of circulation. It has been employed fraudulently to induce symptoms simulating heart disease.

Animal experiments have indicated that prolonged administration of digitalis frequently produces degenerative or hemorrhagic lesions in the cardiovascular and central nervous systems suggestive of local ischemia. It has not been established that such lesions occur in man. However, it is of interest to note that recent studies in man have indicated that digitalis administration leads to a reduction in the clotting time of the blood which may predispose to thrombosis and emboli formation.

Patients receiving digitalis are unusually sensitive to epinephrine and to intravenous calcium. These drugs should be avoided or used with extreme caution during digitalis therapy.

**Standardization of Digitalis and Related Preparations.** Preparations of digitalis are assayed biologically. The United States Pharmacopoeial Digitalis Reference Standard, which is equipotent to the International Digitalis Standard, contains 1 unit of activity in 0.1 Gm. The official method of assay employs the etherized cat as the test object (see Chapter 3). The main criticisms of this method are that it is a measure of the toxicity of the preparations, which is not necessarily related to their therapeutic effect, and that it employs intravenous injection, eliminating the factors of degree and rate of absorption, which are of great significance in oral therapy. Numerous attempts have been made to introduce reliable chemical methods of assay for digitalis preparations. The most reliable method is based on the

Bajet reaction, which depends on the presence of the active hydrogen in the unsaturated lactone group characteristic of cardiac glycosides. Some workers prefer to standardize preparations on patients but this method requires extensive clinical facilities to provide a uniform group of patients. The purified glycosides, digoxin, ouabain and lanatoside-C, being apparently chemical entities, can be identified by chemical and physical means. Preparations of these compounds, however, must be standardized biologically against the respective standard preparation since the amounts present in the accepted dosage forms are too small for adequate physical or chemical identification. Digitoxin must be assayed biologically against the U.S.P. Digitoxin Reference Standard.

## QUINIDINE

Quinidine, the dextrorotatory isomer of quinine, was first used for the treatment of cardiac arrhythmias by Frey in 1918. For many years, cinchona preparations were claimed to act as heart "tonics," but it was not until 1914 that the matter was investigated critically by Wenckebach. He demonstrated conclusively the value of quinine in the treatment of paroxysmal auricular fibrillation. Subsequently, Frey showed that quinidine was superior to quinine by virtue of its greater effect on the heart and its lesser toxicity in therapeutically effective dosage.

Quinidine is widely used in the treatment of auricular fibrillation and auricular flutter. It apparently has a direct depressant action on the heart muscle, causing an increase in the refractory period and a decrease in irritability and in the rate of conductivity. Since the effect is usually greater on the rate of conductivity than on the refractory period, the effect of quinidine is to extinguish the rapid self-perpetuating ring of excitation, the "circuit movement" responsible for the initiation of the rapid rhythm. Quinidine is also of value in the treatment of paroxysmal ventricular tachy-



cardia, postoperative thyroid tachycardia, extrasystoles and paroxysmal auricular tachycardia.

Quinidine is rapidly metabolized and eliminated from the body and there is little danger of cumulative poisoning unless large doses are given at very frequent intervals.

**Toxicity.** Since some individuals are sensitive to quinidine, the initial dose should be small. The more serious complications of quinidine therapy include collapse with cardiorespiratory failure; ventricular fibrillation, which may be prevented by the concomitant administration of digitalis; and the dislocation of emboli following resumption of the normal beat in chronic auricular fibrillation. Rarely, there may be severe gastro-intestinal upsets which make oral administration impracticable. In such cases, quinine preparations may be given parenterally, since quinidine salts, because of their insolubility, can only be injected with large volumes of fluid. Recently an injectable form of quinidine, quinidine hydrochloride with urea and antipyrine, has been described which is said to produce much more prompt effects than oral quinidine and to have an almost equal duration of action. However, intravenous injection of quinidine is dangerous and is rarely justified.

### XANTHINE DERIVATIVES

The xanthine derivatives have already been discussed as diuretics (chap. 15) and central-nervous stimulants (chap. 10). Their value in the treatment of heart disease is due both to their diuretic action and to their stimulatory effect on the myocardium. There is some disagreement as to whether the latter effect is due to a direct action on the myocardium or whether it arises secondarily from an increased coronary flow.

The xanthines have been used since 1895 in the treatment of angina pectoris, though their value has frequently been questioned. Theobromine and theophylline preparations appear to be the most effective. Aminophylline

(theophylline ethylenediamine, euphyllin) is probably the most widely used preparation because of its ready solubility. There is also experimental evidence to indicate that ethylenediamine enhances the vasodilator effect of theophylline without having any such effect of its own.

The xanthines in larger doses cause nausea, heartburn and gastric irritation. More disturbing symptoms include headache, giddiness, nervousness and palpitation. Deaths have been reported from the intravenous administration of aminophylline so that the oral or intramuscular route should be used wherever possible. However, intravenous administration has often proved to be a lifesaver in paroxysmal dyspnea. The use of xanthines in hypertension has no reliable clinical basis. Any fall in blood pressure that these drugs may produce is of short duration and of a minor degree.

## NITRITES AND ORGANIC NITRATES

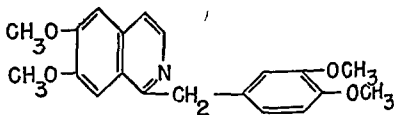
Nitrites and organic nitrate preparations are used chiefly in relieving angina pectoris by their dilating action on the coronary arteries. In view of their direct relaxing action on the smooth muscle of the vascular system and of the bronchioles, they have also been used in the treatment of hypertension and of bronchial asthma, respectively. Their value in hypertension is questionable since their depressant effect is unpredictable and not sustained and tolerance frequently develops after repeated administration.

The beneficial effect of amyl nitrite in angina pectoris was first observed by Lauder Brunton in 1867. This drug is a volatile compound which is dispensed in thin-walled glass ampoules ("pearls") enclosed in a protective cloth envelope. The effects on inhalation are immediate but evanescent. More prolonged though less rapid effects are produced by sodium nitrite taken by mouth, and by some organic nitrates such as erythrityl tetranitrate and mannitol hexanitrate. It has been suggested that the activity of the latter compounds

is due to their degradation in the body to nitrites. However, the rapidity of the onset of their action following intravenous injection and the high degree of potency of some of these preparations suggest that their activity is vested in the intact molecule.

Toxic reactions to nitrites and nitrates include a throbbing headache, weakness, giddiness and faintness. Cyanosis may be present because of the formation of methemoglobin by the nitrite ion. A number of organic nitrate preparations, such as glyceryl trinitrate, erythrityl tetranitrate and mannitol hexanitrate, are explosive and should be stored and handled with care.

### PAPAVERINE



Papaverine is a member of the narcotine group of morphine alkaloids (chap. 9). It was first isolated by Merck in 1848. While its central effects are much less marked than those of morphine, it does have a mild sedative action in therapeutic doses. It is apparently free from addicting properties.

The chief pharmacologic action of papaverine is inhibition of the contractions and relaxation of the tonus of smooth muscle. It was first used clinically by Pal in Vienna in 1914 in conditions of smooth-muscle hyperexcitability, such as gastro-intestinal spasm and biliary colic. Pal also suggested its value in angina pectoris, but its subsequent use by a number of investigators yielded for the most part disappointing results, possibly because of inadequate dosage. During the past 10 years interest in the use of papaverine in heart

conditions has been revived. It has been shown that in suitable oral or intravenous dosage, it effectively dilates the coronary arteries and relieves the arterial spasm accompanying acute vascular occlusion. In addition, Elek and Katz have reported that the drug depresses the conductivity of the heart and eliminates or reduces premature systoles without depressing the myocardium.

## DRUG THERAPY OF HYPERTENSION

A variety of drugs have been recommended for the treatment of hypertension either on the basis of a long-standing popular reputation or because of their pharmacologic action in lowering blood pressure. The results have usually been disappointing and as yet no drug is available which regularly produces a sustained lowering of blood pressure in hypertensive patients without producing toxic symptoms. On occasion, however, subjective improvement may be attained without reference to any alteration in the blood pressure, which may justify continuation of the treatment. Preparations used in the treatment of hypertension include miscellaneous plant and animal extracts of questionable value, such as extracts of mistletoe, garlic, watermelon seeds and extracts of liver, spleen and pancreas; sedatives, such as barbiturates and chloral hydrate; vasodilators, such as nitrates, nitrites and parasympatholytic agents; xanthine derivatives; and thiocyanates.

Thiocyanates. Thiocyanates have been used in Germany in the treatment of hypertensive patients since 1900. Elsewhere, their toxicity was generally considered a barrier to their use until Barker in 1936 demonstrated that the toxic effects could be obviated if the blood level of the drug was not permitted to exceed 15 mg. per 100 cc. The therapeutic range is generally considered to be from 5 to 12 mg. per 100 cc. Both sodium and potassium salts have been used. Thiocyanates are normally present in the body in much higher concentration than any other known depressive substance.

This has led to the suggestion that they play a physiologic role in the regulation of blood pressure.

The mode of action of thiocyanates in lowering the blood pressure is not understood. The action is not readily observed in experimental animals. Claude Bernard in 1857 demonstrated a depressing action of the thiocyanates on the heart but this depression apparently only occurs with near-lethal doses. A depressant action on the adrenal medulla with suppression of epinephrine secretion has been suggested. Toxic effects include dermatologic lesions, nausea, heartburn, and mental disturbances, such as hallucinations, slurred speech and unsteady gait.

In effective thiocyanate therapy, the fall in blood pressure develops slowly, usually after several weeks of treatment. Because of their toxicity and unreliability, thiocyanates should be tried only under strict medical supervision, which must include a check of the blood level of the drug.

Thiocyanates may be of value in the prevention or alleviation of migraine if given in the preheadache stage of an attack. They are of no value after the onset of a headache, presumably because of the slowness with which they act.

No thiocyanate preparations are included in the United States or British Pharmacopoeias or in New and Nonofficial Remedies.

### PREPARATIONS

(For xanthine preparations, see Chapters 10 and 15.)

Digitalis U.S.P. Digitalis leaf B.P. Dried leaf of *Digitalis purpurea* Linné.

Powdered digitalis U.S.P. 0.1 Gm. equivalent to 1 U.S.P. digitalis unit.

Powdered digitalis B.P. 0.1 Gm. equivalent to 1 international standard digitalis unit.

Digitalis tincture U.S.P. Contains 1 U.S.P. digitalis unit per cc.

Tincture of digitalis B.P. Contains 1 international standard digitalis unit per 1 cc.  
Fresh infusion of digitalis B.P. 0.05 international standard unit in 1 cc. 30-120 cc.  
Digitalis injection U.S.P. Usually contains 1 U.S.P. unit of digitalis in either 1 or 2 cc.

Digitalis tablets U.S.P. Digitalis capsules U.S.P. Usually contain 50 and 100 mg. powdered digitalis.  
Digalen N.N.R. Cardioactive principles of digitalis in tablets or injectable solution.

Digitalin N.N.R. Contains therapeutically desirable constituents of digitalis in more absorbable form than whole-leaf preparations. Suitable for oral or parenteral administration.

Digipoten N.N.R. Mixture of digitalis glycosides in soluble form, with an activity equal to that of digitalis leaf of standard quality.  
Digitalin "German" N.N.R. A mixture of glycosides obtained from digitalis seeds, considerably more potent than digitalis.

Digital N.N.R. Fat-free tincture of digitalis.  
Digital N.N.R. Purified extract of digitalis, in which 85 per cent of the inactive ingredients have been removed.

Digitaloxin U.S.P. 0.1 mg.  
Digitaloxin injection U.S.P. Usually 0.2 mg. in 1 cc. and 0.4 mg. in 2 cc.  
Digitaloxin tablets U.S.P. Usually 0.1 and 0.2 mg. tablets.

Digitaine Nativele N.N.R. (digitoxin).  
Gitalin (amorphous) N.N.R. 0.5 mg.  
Lanatoside-C U.S.P. 0.5 mg.  
Lanatoside-C injection U.S.P. Usually available as 0.4 mg. in 2 cc. and 0.8 mg. in 4 cc.

Lanatoside-C tablets U.S.P. Usually 0.5 mg. tablets.  
Digoxin U.S.P. 0.5 mg.

Digoxin tablets U.S.P. Usually 0.25 mg. tablets.  
Digoxin injection U.S.P. Usually 0.5 mg. in 1 cc.

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Powdered digitalis U.S.P. 0.1 Gm. equivalent to 1 U.S.P. digitalis unit.

Powdered digitalis B.P. 0.1 Gm. equivalent to 1 international standard digitalis unit.

Digitalis tincture U.S.P. Contains 1 U.S.P. digitalis unit per cc.

Spirit of glyceryl trinitrate B.P. Contains approximately 1 per cent glyceryl trinitrate in alcohol, 0.06 cc. (in-  
halation).  
Glyceryl trinitrate tablets U.S.P.; B.P. Usually 0.3, 0.4,  
0.6 and 1.2 mg. 0.4 mg.  
Papaverine hydrochloride U.S.P. 0.1 Gm.  
Papaverine-hydrochloride injection U.S.P. Usually 30 mg.  
in 1 cc. 0.1 Gm. (intravenous).

## BIBLIOGRAPHY

## GENERAL

Gold, H.: Pharmacologic basis of cardiac therapy, J.A.  
M.A. 132:547, 1946.  
Levy, R. L.: The drug therapy of cardiac arrhythmias,  
J.A.M.A. 115:848, 1940.

## DIGITALIS AND RELATED PREPARATIONS

Cushny, A. R.: The Action and Uses in Medicine of Digi-  
talis, London, Longmans, 1925.  
Stoll, A.: The Cardiac Glycosides, London, Pharm.  
Press, 1937.  
Withering, William: An Account of the Foxglove and  
Some of Its Medical Uses, Birmingham, 1785.  
Bell, F. K., and J. C. Krantz, Jr.: A chemical evaluation  
of digitalis, J. Pharmacol. & Exper. Therap. 83:213,  
1945.  
Carroll, R. D.: Visual symptoms caused by digitalis, Am.  
J. Ophth. 28:373, 1945.  
Climenko, D. R.: Pharmacodynamics of the cardioactive  
principles of *Urginea maritima* (Squill). J. Am. Pharm.  
A. 27:596, 1938.  
Elderfield, R. C.: The chemistry of the cardiac glyco-  
sides, Chem. Rev. 17:187, 1935.  
De Graff, A. C.: Clinical comparison of the cardiac gly-  
cosides, New York State J. Med. 45:1803, 1946.  
Gold, H., M. Cattell, N. T. Kwit and M. Kramer: The  
relative activity of digitalis preparations in the frog,  
the cat, and man, and its bearing on the problem of  
bio-assay and so-called deterioration, J. Pharmacol. &  
Exper. Therap. 73:212, 1941.



Digilanid N.N.R. A mixture of lanatosides-A, -B, and -C obtained from *D. lanata* in the same proportions in which they occur in the crude drugs. 0.4–0.8 mg.

Tincture of strophanthus B.P. Activity equivalent to that of 0.42 per cent solution of international standard ouabain or 0.33 per cent solution of anhydrous ouabain. 0.12–0.3 cc.

Ouabain U.S.P.; G-strophanthin B.P. Glycoside obtained from seed of *Strophanthus gratus*. 0.25 mg. (intravenously).

Ouabain injection U.S.P. Usually available as 0.25 mg. and 0.5 mg. ouabain per cc.

Scilla B.P. Bulb of *Urginea scilla* (*Urginea maritima*). (*Urginea indica* was acceptable as a war emergency measure.) 0.06–0.2 Gm.

Vinegar of squill B.P. 10 per cent solution of squill in dilute acetic acid.

Syrup of squill B.P. Contains approximately 4.5 per cent squill.

Oxymel of squill B.P. Contains approximately 5 per cent squill.

Tincture of squill B.P. Contains approximately 10 per cent squill.

Scillaren N.N.R. A mixture of the glycosides scillaren-A and scillaren-B in the proportions in which they exist in fresh crude squill. Administered orally. 0.8–1.6 mg.

Scillaren-B N.N.R. The amorphous glycoside of *Scilla maritima*. Administered intravenously. 0.5 mg.

Quinidine sulfate U.S.P.; B. P. 0.2–0.4 Gm.

Quinidine-sulfate tablets U.S.P. Usually 0.1, 0.2 and 0.3 Gm.

Sodium nitrite U.S.P.; B.P. 60 mg.

Sodium-nitrite tablets U.S.P. Usually 30 and 60 mg.

Amyl nitrite U.S.P.; B.P. 0.2 cc. (inhalation).

Erythrityl-tetranitrate tablets U.S.P.; B.P. Usually 15 and 30 mg. 30 mg.

Mannitol hexanitrate N.N.R. 15–60 mg.

- McMahon, A., and R. A. Nussbaum: The use and abuse of theophylline and its derivatives, Southern M. J. 33: 1127, 1940.
- Merrill, G. A.: Aminophylline deaths, J.A.M.A. 123: 1115, 1943.
- Smith, F. M., H. W. Rathe and W. D. Paul: Theophylline in the treatment of disease of the coronary arteries, Arch Int. Med. 56: 1250, 1935.

## NITRITES AND ORGANIC NITRATES

- Crandall, L. A., Jr., C. D. Leake, A. S. Loevenhart and C. W. Muehlberger: Acquired tolerance to and cross tolerance between the nitrous and nitric acid esters and sodium nitrite in man, J. Pharmacol. & Exper. Therap. 41: 103, 1931.
- Marshall, C. R.: The mode of action of nitric esters, J. Pharmacol. & Exper. Therap. 83: 106, 1945.
- Weaver, J. C., J. H. Wills and H. C. Hodge: The effect on the blood pressure of normal persons and hypertensive patients of glyceryl trinitrate, sodium nitrite, erythrol tetranitrate and mannitol hexanitrate, Am. Heart J. 28: 601, 1944.
- Weiss, S., and L. B. Ellis: Influence of sodium nitrite on the cardiovascular system and on renal activity in health, in arterial hypertension and in renal disease, Arch. Int. Med. 52: 105, 1933.

## PAPAVERINE

- Elek, S. R., and L. N. Katz: Some clinical uses of papaverine in heart disease, J.A.M.A. 120: 434, 1942.
- Macht, D. I.: On the relation between the chemical structure of the opium alkaloids and their physiological action on smooth muscle with a pharmacological and therapeutic study of some benzyl esters, I, on the relation of the chemical structure of the opium alkaloids to their action on smooth muscle, J. Pharmacol. & Exper. Therap. 11: 389, 1918.
- de Takats, G.: The use of papaverine in acute arterial occlusions, J.A.M.A. 106: 1003, 1936.

- Hedley, O. F.: The fraudulent use of digitalis to simulate heart disease, *Ann. Int. Med.* 18:154, 1943.
- Herrmann, G. R., G. M. Decherd and W. F. McKinley: Digitalis poisoning, *J.A.M.A.* 126:760, 1944.
- Hueper, W. C.: Some toxic aspects of digitalis therapy. *New York State J. Med.* 45:1442, 1945.
- Jacobs, W. A.: The chemistry of the cardiac glucosides. *Physiol. Rev.* 13:222, 1933.
- Kisch, B.: *Strophanthin*, New York, Brooklyn Medical Press, 1944.
- Macht, D. I.: Experimental studies on heparin and its influence on toxicity of digitaloids, Congo red, cobra venom and other drugs, *Ann. Int. Med.* 18:772, 1943.
- Movitt, E. R.: *Digitalis and other cardiotonic drugs*. Oxford Medical Publications, 1946.
- Stoll, A.: The genuine cardiac glucosides, *J. Am. Pharm. A.* 27:761, 1938.
- de Takáts, G., R. A. Trump and N. C. Gilbert: The effect of digitalis on the clotting mechanism, *J.A.M.A.* 125:840, 1944.

### QUINIDINE

- Carter, J. B.: Uses and abuses of quinidine, *M. Clin. North America* 29:215, 1945.
- Lewis, T.: The value of quinidine in cases of auricular fibrillation and methods of studying the clinical reaction, *Am. J. M. Sc.* 163:781, 1922.
- Sagall, E. L., C. D. Horn and J. E. F. Riseman: Studies on the action of quinidine in man, 1, measurement of the speed and duration of the effect following oral and intramuscular administration, *Arch. Int. Med.* 71:460, 1943.

### XANTHINE DERIVATIVES

- Boyer, N. H.: Aminophylline and related xanthine derivatives, present status and therapeutic claims, *J.A.M.A.* 122:306, 1943.
- Gold, H., N. T. Kwit and H. Otto: The xanthines (theobromine and aminophylline) in the treatment of cardiac pain, *J.A.M.A.* 108:2173, 1937.
- LeRoy, G. V., and J. H. Speer: A comparison of the coronary vasodilator activity of certain alkyl xanthines, *J. Pharmacol. & Exper. Therap.* 69:45, 1940.

Edema (dropsy) is the accumulation of an ultrafiltrate of blood plasma in the intercellular spaces and in serous cavities. Edema may result from a decrease in the osmotic pressure of the plasma or from an increase in capillary pressure. It usually disappears when the underlying disease is treated. If the symptoms are severe, diuretics may be used for temporary relief. If the underlying cause of the edema is a lowering of the blood osmotic pressure, as in glomerulonephritis or malnutrition, diuresis may be induced by transfusions of whole blood, plasma or serum albumins, or gum-acacia solution and the administration of a high-protein—low-salt diet. If the edema is due to an increased capillary pressure, as in congestive heart failure

in the kidney tubules. more dilute in order to prevent the precipitation of drugs accumulated metabolic products and to render the urine edema, to hasten the excretion of ingested poisons, to remove pressure or electrolyte balance of the plasma (water, curial diuretics) or indirectly by alterations in the osmotic either by a direct action on the kidney (xanthine and mercurial filtration or a decrease in tubular reabsorption, by the kidney. Diuresis may be effected by an increase in Diuretics are drugs which increase the excretion of urine

## INTRODUCTION

INTRODUCTION	CRYSTALLOID DIURETICS	XANTHINE DIURETICS
MERCURIAL DIURETICS	PREPARATIONS	

## Diuretics

## DRUG THERAPY OF HYPERTENSION

- Barker, M. H., H. A. Lindberg and M. H. Wald: Further experiences with thiocyanates, clinical and experimental observations, *J.A.M.A.* 117:1591, 1941.
- Evans, W., and D. Loughnan: The drug treatment of hyperpiesia, *Brit. Heart J.* 1:199, 1939.
- Forster, R. E.: The medical use of thiocyanates in the treatment of arterial hypertension, *Am. J. M. Sc.* 206:668, 1943.
- Kapernick, J. S.: The blood pressure in essential hypertension; effect of several reputedly hypotensive drugs, *Am. Heart J.* 26:610, 1943.
- Nelson, E. E.: Thiocyanates, *Internat. M. Digest* 41:245, 1942.

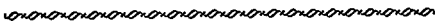
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INTRODUCTION

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Diuretics



or cirrhosis of the liver, saline, xanthine or mercurial diuretics are indicated. If the accumulation of fluid in the chest seriously embarrasses the work of the heart or lungs, it should be removed by paracentesis.

Diuretics are not effective in the presence of severe cardiac or renal damage since urine formation requires adequate blood pressure and blood flow and also a functioning kidney. Injudicious use of diuretics may lead to dehydration or to chloride depletion. In such cases, anuria or oliguria may arise because of the lack of salt to aid in the excretion of water. Hence, edema will persist despite the use of additional diuretics. Occasionally, if diuretics are used during or shortly after digitalis therapy, they may cause a mobilization of digitalis in the body and precipitate digitalis poisoning.

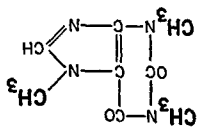
### CRYSTALLOID DIURETICS

Water is an effective diuretic agent and has even been used for the treatment of severe edema. It requires in its passage through the kidneys a certain amount of salt, which it abstracts from the tissues. This, in turn, leads to the excretion of additional water since the isotonicity of the blood must be maintained. In the normal individual, excessive fluid intake may lead to salt depletion.

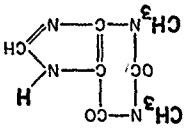
The most effective *saline diuretics* are those with stable ions and those which are more or less foreign to the body; thus the order of effectiveness is potassium, ammonium, sodium, and nitrate, chloride, bicarbonate, acetate and citrate. Potassium nitrate, introduced by Willis in 1679, is the most effective saline diuretic though doses of 12 Gm. or more a day are required. *Isotonic saline* is the most satisfactory agent for producing a profuse diuresis in order to counteract stone formation, to irrigate the urinary tract in infections or to hasten the excretion of toxic substances. Substances such as *urea* and parenterally administered *sucrose*, which are readily filtered by the glomeruli but

poorly reabsorbed by the tubules, cause a diuresis by inhibiting the tubular absorption of water. Urea is probably the least toxic diuretic agent, but large doses are required and its bitter taste is objectionable to many patients. Sucrose is used to reduce cerebral edema since it does not pass the cerebrospinal barrier. A characteristic foamy swelling of the convoluted tubules has been described in man and laboratory animals following large doses. While the effect of these lesions on renal function is not known, it is probably inadvisable to give sucrose in the presence of renal damage or to give repeated injections of sucrose at close intervals.

XANTHINE DIURETICS

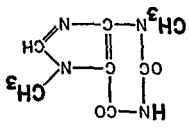


Caffeine



Theophylline

Theobromine



Theophylline and theobromine are among the oldest and safest diuretics. Caffeine is a less effective diuretic agent and has a more marked central-stimulating effect, which is usually undesirable. Theophylline causes a greater diuresis than theobromine. Its action is not so long-lasting, how-





and was soon replaced by less toxic and more efficient preparations, such as *mersalyl* (salyrgan) and *mercurin* (novurit). In these compounds the mercury is present in a side chain, while in merbaphen the mercury is united directly to the benzene ring. The diuretic activity of mercurial diuretics is due largely if not entirely to the action of liberated mercury on the renal tubules, leading to a decreased absorption of water.

Since the xanthine diuretics apparently act mainly on the glomeruli and the mercurials on the tubules, it was not long before the two were combined with a view to obtaining a more effective diuretic agent. The first such preparation was *mercuriophylline* (mercupurin), which was introduced in 1927. It contains theophylline and the free acid of mercurin (*mercuri compound*). *Meralluride* (*merculhydri*) is a similar type of compound. The addition of theophylline to organic mercurials not only increases the efficacy of these preparations but also decreases the local necrosis and inflammation at the site of injection and, in some instances, reduces their toxicity.

Mercurial diuretics can be administered intravenously, intramuscularly, orally or rectally. Their efficacy is enhanced if they are preceded by acid-forming salts, such as ammonium chloride or nitrate. By injection, 1 or 2 cc. of a 10 per cent solution may be given once or twice a week over long periods of time without any apparent damage to the kidney. Occasionally, however, there may be idiosyncrasies or untoward reactions so that it is advisable to give only a small dose at first. Mercurials given rectally in the form of suppositories are not very reliable and may cause irritation of the bowel. Oral administration is fairly effective, the drugs being administered in enteric-coated pills. If they do not prove effective by this route, intramuscular or intravenous injection should not be attempted for several days lest delayed absorption from the bowel lead to toxic symptoms. Mercurials should not be given if there is severe

renal damage since slow excretion may give rise to chronic mercury poisoning.

**Toxicity.** Toxic reactions to mercurial diuretics include dyspnea, substernal oppression, cyanosis, sweating, bradycardia and syncope. Sudden death may occur, due apparently to a direct action of mercury on the ventricular muscle causing fibrillation. Some protection to the heart is said to be offered by small doses of magnesium sulfate. Late toxic effects are characteristic of chronic mercury poisoning (mercurialism) and include stomatitis, salivation, colitis and degeneration of the kidney tubular epithelium.

### PREPARATIONS

Urea U.S.P.; B.P. 20-40 Gm.

Ammonium chloride U.S.P.; B.P. 3-6 Gm.

Potassium acetate U.S.P.; B.P. 1-4 Gm.

Potassium citrate U.S.P.; B.P. 1-2 Gm.

Potassium nitrate B.P. 0.3-1 Gm.

Theophylline U.S.P.; B.P. 0.2 Gm.

Theophylline tablets U.S.P. Usually 100 and 200 mg. tablets.

Aminophylline U.S.P.; B.P. 0.1-0.2 Gm.

Aminophylline injection U.S.P. Usually available containing the following amounts of theophylline ethylenediamine: 0.25 Gm. in 10 cc.; 0.5 Gm. in 2 cc., and 0.5 Gm. in 20 cc.

Aminophylline tablets U.S.P. Usually 0.1 and 0.2 Gm. tablets.

Theophylline and sodium acetate U.S.P.; B.P. 0.2 Gm.

Theophylline and sodium-acetate tablets U.S.P. Usually 0.1 and 0.2 Gm. tablets.

Theobromine and sodium acetate U.S.P.; B.P. 0.5 Gm.

Theobromine and sodium-acetate tablets U.S.P. Usually 0.1 and 0.2 Gm. tablets.

Theocalcin N.N.R. Mixture of calcium theobromine and calcium salicylate. 0.5-1 Gm.

Mersalyl and theophylline injection U.S.P.; injection of mersalyl B.P. Contains approximately 0.1 Gm. of mersalyl and 0.05 Gm. of theophylline per cc. 1-2 cc.  
 Mercurophylline injection (mercupurin) U.S.P. 0.5-1 cc.  
 Meralluride-sodium solution N.N.R. 1-2 cc.

## BIBLIOGRAPHY

### GENERAL

Marvin, H. M.: The therapy of dropsy, J.A.M.A. 114: 757, 1940.  
 Poll, D., and J. E. Stern: Untoward effects of diuretics (with special reference to mercurial diuretics), Arch. Int. Med. 58: 1087, 1936.  
 Smith, H. W.: The physiology of the kidney, New York, Oxford, 1937.

### CRYSTALLOID DIURETICS

Anderson, W. A. D., and W. R. Bethea: Renal lesions following administration of hypertonic solutions of sucrose, J.A.M.A. 114: 1983, 1940.  
 Schemm, F. R.: A high fluid intake in the management of edema, especially cardiac edema, Ann. Int. Med. 21: 937, 1944.

### MERCURIAL DIURETICS

Barker, M. H., H. A. Lindberg and M. E. Thomas: Sud-den death and mercurial diuretics, J.A.M.A. 119: 1001, 1942.  
 Batterman, R. C., A. C. De Graff and J. E. McCormack: The effectiveness and safety of mercupurin adminis-tered orally in the treatment of congestive heart fail-ure, J.A.M.A. 124: 1243, 1944.  
 Brown, G., L. Friedfeld, M. Kissin, W. Modell and R. M. Sussman: Deaths immediately following the intra-venous administration of mercupurin, J.A.M.A. 119: 1004, 1942.  
 Modell, W.: The optimal dose of mercurial diuretics, Ann. Int. Med. 20: 265, 1944.  
 Pines, I., A. Sanabria and R. T. Hernandez Arriens: Mercurial diuretics—the addition of magnesium sul-

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# Blood, Blood Derivatives and Blood Substitutes

16

INTRODUCTION  
WHOLE BLOOD  
BLOOD DERIVATIVES  
BLOOD SUBSTITUTES  
PREPARATIONS

## INTRODUCTION

This chapter includes a discussion of blood, blood derivatives and blood substitutes which are administered parenterally to maintain the circulating blood in shock due to hemorrhage, trauma or burns or to correct hypoproteinemia. Amino-acid preparations, which are administered primarily to supply nutrition, are discussed in the chapter on vitamins. The increased demands for transfusion fluids during the second World War stimulated development of more economical methods of utilizing blood and led to the fractionation of plasma into albumins, used in shock, hypoproteinemia and edema, and a miscellaneous assortment of clinically useful substances, such as gamma globulins, isohemagglutinins, fibrin foam and thrombin. These miscellaneous substances are also included in this chapter.

## WHOLE BLOOD

While the use of blood transfusions dates back to the seventeenth century, the procedure was not put on a safe

phate to prevent the toxic effects of their intravenous administration, Brit. Heart J. 6:197, 1944.

Ruskin, A., and G. R. Herrmann: Studies in combined diuretic therapy, J. Lab. & Clin. Med. 29:486, 1944.

Wexler, J., and L. B. Ellis: Toxic reactions to the intravenous injection of mercurial diuretics, Am. Heart J. 27:86, 1944.

Immediate symptoms of hemolytic reactions due to the transfusion of incompatible blood include chills, fever, nausea, vomiting and defecation and lumbar pain. Renal complications may develop later, and if death results it is usually due to uremia. Treatment for transfusion accidents is symptomatic.

Blood should be taken only from healthy donors, since blood transfusions have been responsible for the transmission of diseases, including malaria, syphilis and infectious jaundice. Care should be taken to avoid air embolism, which may occur as a result of faulty technic either in withdrawing or in administering blood. Filtration should be carried out immediately before injection in order to remove any particles that may cause emboli.

Occasionally, allergic reactions may follow the administration of whole blood and also of plasma and serum. Symptoms include urticaria, edema and asthma. In some cases, these are due to allergens in the blood of the donor, hence blood for transfusion should be taken only from fasting individuals.

## BLOOD DERIVATIVES

Plasma and Serum. The use of plasma became widespread during World War II since it offered certain practical advantages over whole blood. It can be stored for at least 2 years in a liquid, frozen or dehydrated state. It is much less bulky than whole blood and, if pooled plasma is used, large volumes can be administered without cross-matching. It is of special value in cases of shock from severe injury, burns or infections accompanied by loss of plasma from the circulating blood. It is of less value in the loss of large volumes of blood by hemorrhage.

Plasma is of great value in nutritional hypoproteinemia, in plasma loss in ascites and in conditions of impaired protein synthesis. However, large volumes are required to combat effectively a low plasma-protein level since plasma cannot be given in concentrated form.



basis until the recognition in 1900 of the existence of various blood groups and the introduction in 1914 of the relatively nontoxic anticoagulant sodium citrate.

Transfusion of whole blood is the treatment of choice in hemorrhage since it maintains the normal blood volume, prevents hypoxia and shock and maintains the blood-plasma proteins. It is also of value in the treatment of shock from burns, especially if anemia has developed. For immediate treatment, plasma or saline is probably preferable since the fluid, rather than the cellular elements, is lost.

Whole blood retains its usefulness for from 3 to 5 weeks or more if suitably preserved. The prothrombin, however, is destroyed in a few days' time, hence in hemorrhage due to hypoprothrombinemia, fresh blood should be used. Sodium citrate is generally used as an anticoagulant, the final concentration usually being 0.25 per cent. This concentration will not result in toxic symptoms unless large volumes of blood are injected very rapidly. Calcium gluconate is an effective antidote to citrate intoxication. Glucose is frequently added to citrated blood since it has been shown to prolong the life of the red blood cells.

All blood for transfusions should be typed both as regards the Landsteiner groups and the Rh factor. Whenever possible, the patient should receive blood of the same type as his own. Universal group-O type of blood may be used without typing cases of emergency. Such blood may produce untoward effects in patients with type-A or type-B blood since anti-A and anti-B agglutinins and hemolysins occasionally appear in high titer in group-O donors and lead to hemolysis of the recipient's cells. These agglutinins may be neutralized by the addition of A and B group-specific substances, thus minimizing the danger of reactions. With regard to the Rh factor, Rh-negative males should not receive repeated transfusions of Rh-positive blood and Rh-negative women should never receive Rh-positive blood.

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Plasma, like whole blood, should be filtered before being administered, especially since particles of fibrin frequently settle out, leading to the danger of emboli formation or to the blocking of the transfusion needle.

Serum may be used in place of plasma. It has the advantage of not requiring an anticoagulant and of being free from fibrin. However, the red blood cells are wasted during the preparation of serum.

**Red Blood Cells.** During the manufacture of plasma, the red blood cells are usually salvaged and stored in a small quantity of plasma. These may be given in concentrated solution in cases of anemia, especially if cardiac insufficiency exists and unnecessary fluid is to be avoided. They can also be administered after resuspension in saline or glucose solution. Dried red-blood-cell powder has been used as a dressing material in poorly healing wounds but its value has not been adequately established.

**Human Albumin.** Human albumin can be used to raise the osmotic pressure of the blood. Its only advantage over plasma lies in the fact that it can be given in highly concentrated solution, which is of value in patients who may become edematous from excessive volumes of parenteral fluids.

**Miscellaneous Plasma Fractions.** Gamma globulins, a by-product of the fractionation of the plasma proteins, have recently proved of value in preventing or attenuating measles and infectious hepatitis. This preparation is rapidly replacing the use of convalescent serum, pooled normal adult serum and placental extract for the passive immunization in infectious diseases since it is considerably more potent in its content of immune bodies.

Fibrin foam and thrombin is a useful hemostatic agent for the control of local bleeding, especially during brain surgery. The fibrin foam is a porous matrix on which the thrombin, obtained from prothrombin by human thromboplastin, is absorbed. Gelatin has recently been shown to

serve the same purpose as fibrin and has the advantages of being more readily obtainable and more easily handled technically. Fibrin film prepared from fibrinogen and thrombin consists of a thin, rubbery sheet which is used in neurosurgery as a dural substitute or for the prevention of adhesions of the meninges to the brain.

Isohemagglutinins prepared from plasma are available commercially for the typing of blood.

## BLOOD SUBSTITUTES

Crystallloid Preparations. Crystallloid preparations are of value in replacing lost electrolytes, but they diffuse too rapidly to be of any great use as supportive agents in the treatment of hemorrhage or shock. However, sodium chloride, usually in isotonic solution, or Ringer's solution, is often administered routinely to replace fluid lost during surgical procedures, while many advocate the use of saline solutions for the early treatment of burns. Excessive amounts, however, may lead to edema and delayed wound healing.

Other crystallloid preparations are used chiefly for purposes other than blood replacement. Thus, sodium lactate or sodium bicarbonate may be administered to correct acidosis, while glucose solutions are occasionally administered to relieve edema but more often to correct ketosis or disturbances in carbohydrate metabolism.

The use of crystallloid solutions as diuretic agents and for the treatment of cerebral edema is discussed in Chapter 15. Colloidal Solutions. During both World War I and World War II, the heavy demand for transfusions stimulated the search for effective blood substitutes and led to the introduction of solutions of various colloidal preparations in isotonic saline. Such substances to be of value must be capable of forming solutions of a viscosity and osmotic pressure approximately equal to that of normal circulating blood; they must remain in the blood stream for a sufficient period to

give a sustained effect; they must be nonantigenic; and they must not cause any deleterious effects.

While in peacetime the demand for such substances is greatly reduced, they do offer the advantages of being inexpensive, convenient to store and easy to prepare and they can be given without typing or cross-matching. However, at best they are poor alternatives for blood, plasma or serum.

Gum acacia as a 6 per cent solution was widely used during the first World War, especially by the British Army. However, it was later shown to be removed very slowly from the body, being stored largely by the liver and to a lesser extent by the spleen and kidney. It has been said to lead to liver or kidney damage, and while this effect may be due to impurities, the use of acacia as a transfusion fluid has been virtually abandoned. Recently, it has been advocated for the relief of edema in nephritis.

Gelatin was introduced by Hogan in 1915, but it soon became overshadowed by gum acacia. Its value has recently been reinvestigated and it has been shown that suitable gelatin as a 4 per cent to 8 per cent solution produces few untoward effects. It may, however, cause a conglomeration of red blood cells, which interferes with subsequent typing of the blood; hence, a sample of blood for typing purposes should be obtained prior to the injection.

Gelatin supplies a number, but not all, of the essential amino acids, but it is doubtful if it can contribute appreciably to the production of tissue protein unless supplemented with other amino-acid preparations.

Isinglass or "fish gelatin" in 7 per cent solution was suggested early in the recent war as a substitute for animal gelatin since it was thought that impure gelatin preparations might result in tetanus or anthrax infection or might give rise to sensitization. However, with carefully manufactured gelatin, such complications apparently do not arise. One disadvantage of gelatin solutions is that they gel at 20° C.

and hence must be heated prior to administration in cool or temperate surroundings.

Other colloidal substances which have received limited experimental and clinical trials include pectin, polyvinyl alcohol and bovine albumin and plasma. Pectin is a colloidal carbohydrate and is presumably nonantigenic. However, there is some indication that it may act as a reticulo-endothelial irritant. Bovine blood approximates human blood as regards total protein but contains more fibrinogen. While it provides a cheap and readily available source of serum and of albumin, the use of these products is attended by such a high incidence of reactions that it has, for the time being at least, been abandoned.

### PREPARATIONS

Citrated normal human plasma U.S.P. Sterile plasma obtained from pooling approximately equal amounts of the liquid portion of citrated whole blood from eight or more human donors certified free of disease transmissible by blood transfusion (50 cc. of 4 per cent sodium citrate in isotonic sodium chloride per each 500 cc. blood). It may be dispensed as liquid plasma, frozen plasma or dried plasma. 500 cc.

Normal human serum U.S.P. Sterile serum obtained by pooling approximately equal amounts of the liquid portion of coagulated whole blood from eight or more human donors-certified free from any disease transmissible by blood transfusion. 500 cc.

Anticoagulant sodium-citrate solution U.S.P. B.P. Contains 25 Gm. sodium citrate ( $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2\text{H}_2\text{O}$ ) and 9 Gm. sodium chloride in 1,000 cc.

Anticoagulant acid citrate-dextrose solution (A.C.D. solution) U.S.P.

Solution of sodium citrate with dextrose B.P. Each 1,000 cc. contains 30 Gm. sodium citrate and 30 Gm. dextrose.

- Injection of sodium chloride and acacia B.P. Contains 9 Gm. sodium chloride and 17 Gm. acacia in 1,000 cc.
- Ringer's solution (isotonic solution of three chlorides) U.S.P. Contains between 0.84 and 0.88 Gm. NaCl; 25-25 mg. KCl and 30-36 mg.  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  in 100 cc.
- Lactated Ringer's solution U.S.P.
- Isotonic sodium-chloride solution U.S.P. Contains between 0.88 and 0.92 Gm. NaCl in 100 cc.
- Physiologic solution of sodium chloride B.P. Contains 9 Gm. NaCl in 1,000 cc.
- Sodium lactate injection U.S.P.
- Dextrose injection U.S.P.
- Dextrose and sodium-chloride injection U.S.P.

## BIBLIOGRAPHY

### GENERAL

- Abbott, W. E.: A review of the present concepts on fluid balance, *Am. J. M. Sc.* 211: 232, 1946.
- Bradasch, G. A.: Comparative value of various parenteral fluids, *Anesthesiology* 5: 1, 1944.
- Janeway, C. A., W. Berenberg and G. Hutchins: Indications and uses of blood, blood derivatives and blood substitutes, *M. Clin. North America* 29: 1069, 1945.

### WHOLE BLOOD

- Allen, J. G., D. E. Clark, T. T. Thornton and W. E. Adams: The transfusion of massive volumes of citrated whole blood and plasma in man—clinical evidence of its safety, *Surgery* 15: 824, 1944.
- Denstedt, O. F., D. E. Osborne, H. Stansfield and I. Rochlin: The survival of preserved red cells after transfusion, *Anesthesiology* 5: 237, 1944.
- Evans, E. I., and I. A. Bigger: The rationale of whole blood therapy in severe burns, *Ann. Surg.* 122: 693, 1945.
- Hirsh, J.: The story of blood transfusion: its civilian and military history, *Mil. Surgeon* 88: 143, 1941.
- McGraw, J. J., Jr., E. K. Vaubel, J. Reichel, Jr., and J. Elliott: Complications of blood transfusion, *Surg. Clin. North America* 25: 1042, 1945.

- Rappaport, E. M.: Hepatitis following blood or plasma transfusions, observations in thirty-three cases, J.A.M.A. 128:932, 1945.
- Tisdal, L. H., D. M. Garland and A. S. Wiener: A critical analysis of the value of the addition of A and B group-specific substances to group O blood for use as universal donor blood, J. Lab. & Clin. Med. 31:437, 1946.
- Unger, L. J., M. Weinberg and M. Lelkon: The Rh factor as applied to the operation of blood banks, Am. J. Clin. Path. 16:498, 1946.
- Wiener, A. S.: Blood groups and Blood Transfusion, Springfield, Ill., Thomas, 1943.
- Witebsky, E., N. C. Klendshoj and P. Swanson: Preparation and transfusion of safe universal blood, J.A.M.A. 116:2654, 1941.

#### BLOOD DERIVATIVES

- Anderson, M. W., N. W. Barker and T. H. Seldon: A clinical evaluation of powdered red blood cells in the treatment of ulcers of the extremities associated with vascular disorders, Am. Heart J. 32:754, 1946.
- Bailey, O. T., F. D. Ingraham, O. Swenson, J. J. Lowrey and E. A. Bering, Jr.: Human fibrin foam with thrombin as a hemostatic agent in general surgery—experimental studies and clinical use, Surgery 18:347, 1945.
- Binder, M. L., and A. Klein: Concentrated red-cell transfusions, Am. J. M. Sc. 208:95, 1944.
- Blum, L. L.: Isoagglutinin and agglutininogen contents of pooled plasma—their role in transfusion reactions, Am. J. Clin. Path. 14:112, 1944.
- Cohn, E. J.: Blood proteins and their therapeutic value, Science 101:51, 1945.
- Jenkins, H. P., E. H. Senz, H. W. Owen and R. W. Jampolis: Present status of gelatin sponge for the control of hemorrhage, with experimental data on its use for wounds of the great vessels and the heart, J.A.M.A. 132:614, 1946.
- Lozner, E. L., S. Lemish, A. S. Campbell and L. R. Newhouser: Preservation of normal human plasma in the liquid state; V. clinical, chemical and physicochemical studies during three years of storage at room temperature, Blood 1:459, 1946.



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- Blum, L. L.: Isoagglutinin and agglutininogen content of pooled plasma—their role in transfusion reactions, *J. Clin. Path.* 14:112, 1944.
- Cohn, E. J.: Blood proteins and their therapeutic value, *Science* 101:51, 1945.
- Jenkins, H. P., E. H. Senz, H. W. Owen and R. Jampolis: Present status of gelatin sponge for the control of hemorrhage, with experimental data on its use for wounds of the great vessels and the heart, *J.A.A.* 132:614, 1946.
- Lozner, E. L., S. Lemish, A. S. Campbell and L. R. N. houser: Preservation of normal human plasma in liquid state; V. clinical, chemical and physicochemical studies during three years of storage at room temperature, *Blood* 1:459, 1946.

- Miller, E. B., and L. H. Tisdall: Reactions to 10,000 pooled liquid human plasma transfusions, *J.A.M.A.* 128:863, 1945.
- Stead, E. A., Jr., E. S. Brannon, A. J. Merrill and J. V. Warren: Concentrated human albumin in the treatment of shock, *Arch. Int. Med.* 77:564, 1946.
- Stead, E. A., Jr., E. S. Brannon, A. J. Merrill and J. V. Warren: Chemical, clinical and immunological studies on the products of human plasma fractionation (a series of 23 papers), *J. Clin. Investigation* 23:417, 1944.

## BLOOD SUBSTITUTES

- Amberson, W. R.: Blood substitutes, *Biol. Rev.* 12:48, 1937.
- Andersch, M., and R. B. Gibson: Studies on the effects of intravenous injections of colloids—I, deposition of acacia in the liver and other organs and its excretion in urine and bile, *J. Pharmacol. & Exper. Therap.* 52:390, 1934.
- Brunschwig, A., S. Nichols and R. Bigelow: Intravenous gelatin for nutritional purposes—clinical and experimental studies, *Surg., Gynec. & Obst.* 82:25, 1946.
- Johnson, J. B., and L. H. Newman: Intravenous injection of acacia—clinical and physiologic effects on patients with nephrotic edema, *Arch. Int. Med.* 76:167, 1945.
- Koop, C. E., and L. Bullitt: Gelatin as a plasma substitute, the effect of gelatin infusion on the subsequent typing and cross-matching of the blood, with a method of eliminating the phenomenon of pseudoagglutination, *Am. J. M. Sc.* 209:28, 1945.
- Popper, H., B. W. Volk, K. A. Meyer, D. O. Kozoll and F. W. Steigmann: Evaluation of pectin and gelatin solutions used in the treatment of shock: histologic changes produced in the human being, *J. Lab. & Clin. Med.* 30:352, 1945.
- Patek, A. J., Jr., F. E. Kendall, J. Victor, A. Lowell, H. Colcher and D. Seegal: Venous thrombosis after infusion with gelatin solutions containing mercurial preservatives, *Am. J. M. Sc.* 212:561, 1946.

without treatment, which may lead to an unduly early in mind that there may be remissions in these diseases but necessarily prolonging his life. It is important to palliative action, improving the comfort of the patient the erythropoietic and leukopoietic tissues have many of the drugs used in the treatment of diseases or shock is discussed in Chapter 16.

The use of blood itself or of blood substitutes in acute as drugs affecting the coagulability of the blood in the leukemias, Hodgkin's disease and lymphosarcoma (the leukemia vera and anemia) and of the leukopoietic he treatment of diseases of the erythropoietic tissue The drugs discussed in this chapter include those u

## INTRODUCTION

### PREPARATIONS

RADIOACTIVE PHOSPHORUS	ADRIAN THERAPY
NITROGEN MUSTARDS	(FOLIC ACID)
PHENYLHYDRAZINE	ERYTHROCYTAMIC ACID
ARSENIC	EXTRACTS
URETHANE	LIVER AND STOMACH
ANTICOAGULANTS	IRON PREPARATIONS
COAGULANTS	INTRODUCTION

# Drugs Affecting the Blood and the Blood-Forming Organs

tic appraisal of newly introduced drugs. Many of the drugs discussed are unpleasant to take and may cause severe toxic reactions but the severity and the poor prognosis of the diseases usually justify their use and stimulate the search for more effective compounds.

### IRON PREPARATIONS

Preparations containing iron in a form available to the body have long been used in the treatment of hypochromic anemias due to iron deficiency in the body. Symptoms resulting from this deficiency include anemia, weakness and lassitude, which are promptly relieved by adequate oral doses of inorganic iron preparations. Ferrous iron is effective in smaller dosage than ferric and causes less gastric irritation. The addition of copper, manganese or cobalt with a view to enhancing the iron utilization is probably of little or no value, with the possible exception of anemia in infants fed cows' milk exclusively, since the dietary requirements of these elements is so small.

Iron compounds are comparatively nontoxic, the primary effects of overdosage being gastro-intestinal cramps and diarrhea. In solution form, they may cause a black deposit on the teeth which can be readily removed by a toothbrush or avoided if the preparations are taken through a straw.

The manner in which iron restores the blood hemoglobin and the metabolism of iron in the body are not wholly understood. Work with radioactive iron has shown that the amount of iron absorbed is apparently related to the needs of the body for iron. It is not excreted to any appreciable extent by the body. Parenteral administration of iron offers no advantages and may cause local pain, gastro-intestinal effects and occasionally nephritis.

### LIVER AND STOMACH EXTRACTS

Pernicious anemia, a form of anemia due to defective erythrocyte maturation, was first described in detail by

Thomas Addison in 1849. The treatment of this condition, however, remained unsatisfactory until 1926, when Minot and Murphy reported successful results with addition of raw liver to the diet. Their work was prompted by that of Whipple and his associates, who had demonstrated in dogs the blood-regenerating properties of a diet rich in liver. Following the dramatic report of Minot and Murphy, efforts were made to isolate the active antianemic principle or principles of liver. As yet, this goal has not been reached; however, extracts have been sufficiently purified so that the requirement of pernicious-anemia patients are approximately 1 mg. per day, while the corresponding requirement of whole liver is from 200 to 400 Gm.

Purified liver extracts are generally administered intramuscularly. Orally, much larger doses are required. Intramuscular injections are more reliable in severe pernicious anemia since the gastro-intestinal disturbances which accompany this disease may interfere with absorption from the alimentary tract. Intravenous therapy, while possible, offers no advantages. A sensitivity, apparently allergic in nature, may develop to parenteral liver injections. Desensitization may be effected by the administration of small doses. Otherwise, the patient must be placed on oral liver therapy or on desiccated stomach preparations. Occasionally, changing to another brand of liver extract may suffice, especially if the species of animal from which the new preparation is made is also different.

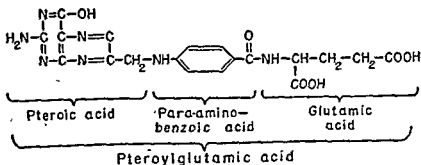
In 1928, Castle, who was interested in the gastric disturbances of pernicious anemia, reported that the disease could be controlled by the administration of beefsteak incubated in normal gastric juice. He suggested that the disease might be due either to the absence of an intrinsic factor present in normal gastric juice, to the absence of an extrinsic factor normally supplied in the food, or to a failure of absorption of the products of interaction between the two factors, which in the normal individual are stored in the body as

the antipernicious-anemia factor or factors. Castle's work led to the introduction of desiccated hog stomach (ventriculin) for the treatment of pernicious anemia. The activity of this preparation may be due to an unidentified intrinsic factor or to the adsorption on the mucosa of a liver principle previously formed by the interaction of extrinsic and intrinsic substances. Its chief value lies in the treatment of patients sensitive to liver extracts.

The site of formation of the intrinsic substance in the human being is thought to be in the fundus glands but the failure of pernicious anemia to develop after total gastrectomy has led to the suggestion that there may be an extra-gastric source as well, unless one assumes a long period of storage.

**Standardization of Antianemia Preparations.** Since pernicious anemia has been observed only in man, there is no method of assay of antianemia preparations using laboratory animals. Standardization must be carried out on untreated pernicious-anemia patients in a state of relapse. A U.S.P. unit is the minimal amount which, when given daily, will cause an adequate hematopoietic response. It is necessary to distinguish between "oral" units and "injectable" units since much smaller doses are effective by injection.

### PTEROYLGLUTAMIC ACID



Pteroylglutamic acid, "folic acid," is a synthetic product prepared by Angier and his associates in 1945. It has given

promising clinical results in the treatment of various types of macrocytic anemia, including pernicious anemia, nutritional macrocytic anemias and sprue. It also acts as an essential metabolite for the growth of certain bacteria, including *Lactobacillus casei* and *Streptococcus lactis*. Its clinical use preceded the disclosure of its chemical nature, and in the interim it became known as both "follic acid" and "synthetic *L. casei* factor" because of its similarity to folic acid isolated in nearly pure form from spinach by Mitchell, Snell and Williams and to the *L. casei* factor isolated from liver by Skokstad. It is probably identical with the latter compound and can be classed as a member of the vitamin B complex.

The relationship of pteroylglutamic acid to the antipernicious anemia factor in liver extract is not fully understood. The activity of liver extract is out of all proportion to its pteroylglutamic acid content; in addition, pteroylglutamic acid is equally potent by mouth and by injection and can be tolerated by persons who have developed a sensitivity to liver extract. It does not appear to be so effective as liver extract in prevention or treatment of neurologic complications in pernicious anemia. Pteroylglutamic acid is evidently not the "extrinsic factor" of Castle since it is effective parenterally in low dosage and also in cases in which the intrinsic factor is absent or greatly reduced.

The advantages of pteroylglutamic acid lie in its cheapness, its effectiveness by the oral route and the apparent nondevelopment of sensitivity on repeated administration. Thymine, a constituent of nucleic acid, has been shown to have a hematopoietic effect in pernicious anemia and sprue when given in very large doses. Spies has suggested that pteroylglutamic acid may act as an enzyme or a co-enzyme in the synthesis of thymine or a thymine-like compound in the body.



## RADIATION THERAPY

Radiation therapy was first introduced for the treatment of blood dyscrasias by Pusey in 1902 and Senn in 1903. It is of established value in such conditions as polycythemia vera, chronic leukemias, lymphosarcoma, Hodgkin's disease, multiple myeloma, endothelioma and Ewing's tumor. Its effects are palliative only, mainly by relieving pain and pressure symptoms from enlarged lymph glands or spleen or from infiltrations of neoplastic growths. The radiation may be directed towards the neoplasm itself or towards the spleen, long bones and chest. Recently "spray" radiation has come into wide use. In this procedure, the whole body, except for the chest and genital organs, is exposed to a low intensity of radiation. The treatments may be given at frequent, regular intervals or a short, intensive treatment may be given and the patient allowed to remain untreated until a recurrence of symptoms develops. The most common untoward effect of radiation therapy is radiation sickness characterized by anorexia, nausea and vomiting. The white-blood-cell count must be followed closely during treatment since leukopenia may develop from excessive radiation.

Excessive total body roentgen therapy may lead to severe hemorrhages. Recently, Allen has reported that the bleeding is apparently associated with an increased output of heparin or heparin-like compounds in the body. His studies indicate that administration of toluidin blue (an antiheparin substance) will control the bleeding by inactivating the heparin, even though the platelet count may have been considerably reduced. Preliminary clinical studies suggest that this dye may also control petechial hemorrhages and thrombocytopenic puerpera, but is ineffective in treatment of prothrombin deficiency and in hemophilia.

## RADIOACTIVE PHOSPHORUS

Radioactive phosphorus ( $P^{32}$ ) was first introduced into medicine in 1936 for the treatment of blood dyscrasias by

Lawrence and his associates. In many respects, its effects are similar to those of radiation therapy but it has several advantages. It is administered intravenously or occasionally orally and is quickly concentrated in rapidly growing tissues, and especially in tissues with a high phosphorus content which metabolize phosphorus rapidly; furthermore, it does not cause radiation sickness, its penetrating powers are limited, and its duration of activity is sufficiently long for all practical purposes and yet short enough to be relatively free from long-range harmful effects. At first, its use was restricted by the limited supplies available but with the recent developments in atomic research, it has become available at fairly low cost. However, at this writing, official restrictions on the distribution of the substance limit its use to such research centers as are equipped with suitable apparatus. (The principles of allocation and distribution of radioactive isotopes are presented in *Science* 103: 697, 1946.)

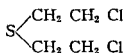
Radioactive phosphorus is probably the treatment of choice in advanced cases of polycythemia vera, long periods of remission being secured by a single course of therapy. It slows the rate of erythropoiesis and improves the physical comfort of the patient, but probably does not prolong life. Its effects develop slowly and the erythrocyte count is usually not appreciably reduced until six weeks after initiation of therapy. Hence, if the symptoms are severe, the patient may have to be bled in order to secure more prompt relief. Phlebotomy alone is often adequate treatment for mild forms of the disease.

Radioactive phosphorus is about as effective as radiation therapy and arsenic preparations in the treatment of chronic myelogenous leukemia but does not cause such a rapid reduction in the size of enlarged lymph nodes or spleen. It may be combined with either form of treatment if symptoms or pressure effects are severe. Radioactive phosphorus is of little or no value in acute or subacute forms of this

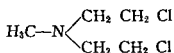
disease, or in the lymphatic leukemias, in Hodgkin's disease, in reticular-cell sarcoma and in lymphosarcoma.

Undesirable effects of radioactive phosphorus therapy include leukopenia, thrombocytopenia and anemia due to the depressant action on the bone marrow. The dosage of the drug is regulated by blood and marrow examinations and by general clinical observations. With adequate precautions, toxic effects can be avoided or minimized. The usual single dose of  $P^{32}$  is one millicurie, a course of treatment including from 3 to 7 such doses. Up to 15 millicuries may be used in a course of treatment for polycythemia vera.

### NITROGEN MUSTARDS



Bis ( $\beta$  chloroethyl) Sulfide  
(Mustard)



Methyl Bis ( $\beta$  chloroethyl) Amine  
(A Nitrogen Mustard)

The clinical value of the nitrogen mustards was first suggested by toxicity studies undertaken both by German and American scientists to determine their possible use as chemical warfare agents. It was found that certain  $\beta$ -chloroethyl compounds of this series were most toxic to areas of rapid growth, such as the hematopoietic system and the intestinal tract. As a result, they have been tried in the treatment of neoplastic diseases, lymphosarcoma and leukemia. The most encouraging effects have been obtained in the treatment of Hodgkin's disease though the results are apparently no better than those obtained by radiation therapy. Results in leukemia have been disappointing.

Toxic effects of the nitrogen mustards include moderate lymphopenia, neutropenia, thrombocytopenia, anemia, occasional bleeding tendencies and nausea and vomiting. The activity of the nitrogen mustards decreases very rapidly after solution in water, hence freshly prepared solutions in

physiologic saline are immediately injected intravenously, usually about 0.1 mg. per Kg. A course of treatment consists of four such injections given on successive days. Cautious handling is necessary to prevent contact of the drug with the skin of the patient or doctor with ensuing discomfort or vesication. Severe tissue damage may occur if leakage is permitted around the injection site.

Numerous analogous compounds of this series have been studied but only those  $\beta$ -chloroethyl compounds which can form a cyclic onium cation are capable of exerting the typical actions described above.

## PHENYLHYDRAZINE

Phenylhydrazine and the less toxic acetyl phenylhydrazine are useful in the treatment of polycythemia vera because of their destructive action on the red blood cell. Phenylhydrazine was first introduced clinically in 1918 by Eppinger and Kloss. Too large doses may precipitate hemolytic crises from massive destruction of red cells, but, if used in moderation, these drugs constitute an inexpensive and easily administered form of treatment. They probably do not cause liver or kidney damage, provided the dosage is carefully controlled. They are best administered by capsule and should be handled with caution since they may give rise to severe dermatitis. Acetyl phenylhydrazine was introduced as an antipyretic under the name of pyrodin but proved too toxic.

## ARSENIC

The ability of inorganic arsenic compounds to lower the leukocyte count in chronic myeloid leukemia was first studied critically in 1878 by Culter and Bradford. Little use has been made of these preparations since the introduction of roentgen therapy; however, there is little question as to their value either as adjuvants to roentgen therapy or as the sole therapeutic agent in leukemia and in the early

treatment of polycythemia vera. The commonly used preparation is arsenic trioxide, either in the form of a solution of arsenious oxide or a solution of potassium arsenite (Fowler's solution). Injudicious use of these compounds may lead to symptoms of chronic arsenic poisoning, including polyneuritis, keratosis and cirrhosis.

### URETHANE



Urethane (ethyl carbamate) has recently been used in England in the treatment of leukemia. The therapeutic effects appear to be essentially similar to those obtained with roentgen therapy. They include a fall in total white-cell count, a tendency for the differential count to approach a more normal pattern, diminution in the size of the spleen and of enlarged lymph nodes and a rise in hemoglobin. Toxic effects are slight, consisting of gastro-intestinal upsets and drowsiness. The therapeutic action of urethane may be associated with its inhibitory effect on mitosis which has been demonstrated with plant and animal cells.

### ANTICOAGULANTS

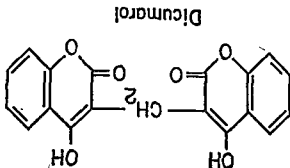
\* Anticoagulation therapy using heparin or dicumarol is a recently introduced method for the prevention of thrombi and emboli, especially in conditions of accidental or surgical trauma. It is of no benefit if the blood clots have already formed except that it may prevent their further extension.

Heparin is an anticoagulant substance present in the tissues of the body. It was isolated from the liver by Howell and Holt in 1916. Its exact chemical nature has not been determined. It may not be a single substance but

rather a mixture of compounds having a mucicoin—polysulfuric acid structure. Heparins from various animal sources have similar chemical properties but differ in their anticoagulant activity.

Heparin apparently forms a strong thrombin-inactivating complex with a co-factor present in serum albumin. It is effective both in vitro and in vivo after parenteral injection. It acts almost immediately but its effects usually last only 3 or 4 hours. It is usually given intravenously but recently a more prolonged action has been obtained by subcutaneous injection of heparin in a gelatinous base which releases the drug slowly.

Various units of potency and methods of assay have been suggested for expressing the activity of heparin extracts. Probably the best standard is that of the crystalline barium salt of heparin prepared by the Connaught laboratories of the University of Toronto. The proposed unit is defined as 0.01 mg. of this salt.

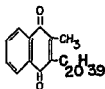


Dicumarol was first isolated from spoiled sweet clover by Link and his associates in 1941. It is the causative agent of a hemorrhagic disease of cattle, "sweet-clover disease," which is due primarily to a prothrombin deficiency. For commercial purposes, dicumarol is prepared synthetically from acetylsalicylic acid. The mode of action of dicumarol is not yet understood. It is believed to inhibit production of prothrombin possibly

by interference with the enzyme system responsible for its elaboration. It is effective *in vivo* but not *in vitro*.

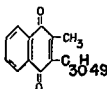
Dicumarol offers the advantages over heparin of being effective on oral administration and of being relatively inexpensive. However, there is usually a delay of about 48 hours before its effect is apparent. Furthermore, its action may persist for several days and cumulative poisoning may occur with hemorrhages as the main toxic effect. It can be readily antidoted with large doses of vitamin K preparations or by blood transfusions. During the administration of dicumarol, the prothrombin level should be followed daily and should not be permitted to fall below from 10 to 30 per cent of the normal. Dicumarol should not be given to patients with hemorrhage tendencies or with liver or kidney disease. When an immediate yet protracted anticoagulant effect is desired, dicumarol may be given together with heparin, the heparin being discontinued as soon as a satisfactory prothrombin level has been reached.

### COAGULANTS



Vitamin K<sub>1</sub>

(From Plants)



Vitamin K<sub>2</sub>

(From Micro-organisms)



Menadione

(Synthetic)

**Vitamin K Preparations.** The existence of an antihemorrhagic factor in green plants was first demonstrated by Dam in 1929. He showed that chicks raised on a deficient diet developed hemorrhagic manifestations which could be alleviated by the addition of alfalfa to the diet. The active principle was isolated simultaneously by Dam and by Doisy in 1939. Subsequently, Doisy isolated a second antihemorrhagic principle from putrified fish meal. This principle apparently does not occur in plants and is known as

vitamin K<sub>2</sub>, while the original principle is known as vitamin K<sub>1</sub>. Both these substances are lipid in nature and are not absorbed from the gastro-intestinal tract in the absence of the bile salts. A number of synthetic naphthoquinones have been found to have vitamin-K-like properties, and, of these, menadione (2-methyl-naphthoquinone) and the water-soluble menadione sodium bisulfite have been accepted for clinical use.

Vitamin K preparations prevent hemorrhages by raising the prothrombin level of the blood. In massive dosage (from 40 to 60 mg.), they effectively antidote dicumarol overdosage and are probably of greatest value in this condition. They will correct hypoprothrombinemia due to such conditions as obstructive jaundice in which the normal absorptions of the vitamin K of the diet is interfered with. They may be of value in hemorrhagic states associated with hepatic disease provided the liver can utilize the administered drug. They were at one time widely advocated as prophylactic and curative agents in hemorrhagic disorders in the newborn. However, the present consensus appears to be that these disorders are not necessarily related to the prolonged prothrombin time characteristic of the first week of life and that their incidence is not significantly reduced by the administration of vitamin K preparations.

## PREPARATIONS

Ferrous sulfate U.S.P.; B.P. 0.3 Gm.

Ferrous sulfate tablets U.S.P. Usually contain 0.3 Gm. ferrous sulfate.

Exsiccated ferrous sulfate U.S.P.; B.P. Contain not less than 80% ferrous sulfate, 0.2 Gm.

Reduced iron B.P. Contains not less than 90% metallic iron. 0.06-0.5 Gm.

Ferric ammonium citrate U.S.P.; B.P. 1 Gm.



Ferric ammonium citrate capsules U.S.P. Usually contain 0.5 Gm. Ferric ammonium citrate.

Iron and quinine sulfate B.P. Contains approximately 13% iron and 15% anhydrous quinine. 0.3-1 Gm.

Pills of ferrous carbonate (Blauds' pills) B.P. Each pill contains not less than 60 mg.  $\text{FeCO}_3$ . 5 pills.

Saccharated iron carbonate B.P. 0.6-2 Gm.

Injection of iron B.P. Contains double salt of citrate of iron and ammonium. (Intramuscular). 1-2 cc.

Syrup of ferrous iodide B.P. Contains 5%  $\text{FeI}_2$ . 2-8 cc.

Compound syrup of ferrous phosphate (Parrish's syrup) B.P. Contains 0.9% anhydrous ferrous phosphate. 2-8 cc.

Syrup of ferrous phosphate with quinine and strychnine (Easton's syrup) B.P. Contains 1.8% anhydrous ferrous phosphate, 1.09% anhydrous quinine and 0.0246% strychnine. 2-4 cc.

Citrated ferrous chloride B.P. 0.2-0.3 Gm.

Ferrous lactate N.N.R. 0.06-1.3 Gm.

Liver extract U.S.P.; B.P. 1 U.S.P. unit.

Liquid extract of liver B.P. Each cc. equivalent to 8 Gm. raw liver. 30 cc.

Liver solution U.S.P. 1 U.S.P. unit.

Liver injection U.S.P. Usually contains 1 and 2 U.S.P. units in 1 cc. injected intramuscularly. 1 U.S.P. unit.

Powdered stomach U.S.P. 1 U.S.P. unit.

Liver with stomach U.S.P. 1 U.S.P. unit.

Extralin N.N.R. A liver-stomach concentrate administered orally. Contains 1 U.S.P. unit in 6 Gm.

Potassium arsenite solution U.S.P. Arsenical solution B.P. (Fowler's solution) approximately 1% solution of arsenic trioxide with potassium bicarbonate. 0.2 cc.

Menadione U.S.P. Menaphthone B.P. 1 mg.

Menadione tablets U.S.P. Usually 1 and 2 mg. tablets.

Menadione sodium bisulfite U.S.P. intravenous or intramuscular. 2 mg.

Menadione sodium bisulfite injection, U.S.P. usually contains the following amounts of menadione sodium bisulfite: 2 mg. in  $\frac{1}{2}$  cc.; 4 mg. in 1 cc.  
Vitamin K<sub>1</sub> N.N.R. 4-10 mg.

## BIBLIOGRAPHY

### GENERAL

A Symposium on the Blood and Blood-forming Organs, Madison, Univer. Wisconsin Press, 1939.  
Abt, H. L.: The treatment of leukemia, Med. Clin. North America 28: 187, 1944.  
Forkner, C. E.: Leukemia and Allied Disorders, New York, Macmillan, 1938.  
Kracke, R. R.: Diseases of the Blood and Atlas of Hematology, 2nd ed., Philadelphia, J. B. Lippincott, 1941.  
Pxaegel, B. L., and J. F. Ross: The diagnosis and treatment of anemia, Med. Clin. North America 30: 1042, 1946.  
Vaughan, J. M.: The Anemias, New York, Oxford, London, Humphrey Milford, 1936.

### IRON THERAPY

Hahn, P. F., W. F. Bale, E. O. Lawrence and G. H. Whipple: Radioactive iron and its metabolism in anemia, J.A.M.A. 111: 2285, 1938.  
Heath, C. W.: Iron in nutrition—requirements for iron, J.A.M.A. 120: 366, 1942.  
Henderson, V. E., and G. H. W. Lucas: On the absorption of iron, Am. J. Digest. Dis. 11: 244, 1944.

### LIVER AND STOMACH PREPARATIONS

Castle, W. B.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia; 1. The effect of the administration to patients with pernicious anemia of the contents of the normal human stomach recovered after the ingestion of beef muscle, Am. J. M. Sc. 178: 748, 1929.  
Fox, H. J., and W. B. Castle: Observations on the etiologic relationship of achylia gastrica to pernicious anemia; IX. Difference in site of secretion of intrinsic factor in the hog and in the human stomach, Am. J. M. Sc. 203: 18, 1942.

- McSorley, J. G., and L. S. P. Davidson: Sensitivity to liver extract, *Brit. M. J.* 1:714, 1944.
- Minot, G. R., and W. P. Murphy: Treatment of pernicious anemia by a special diet, *J.A.M.A.* 87:470, 1926.
- Schwartz, S. O.: Pernicious anemia, *Med. Clin. North America* 28:214, 1944.
- Schwartz, S. O., and H. Légère: Treatment of liver extract sensitivity, *Blood* 1:307, 1946.
- Subbarow, Y., A. B. Hastings and M. Elkin: Chemistry of anti-pernicious anemia substances of liver, *Vitamins and Hormones* 3:237, 1945.

#### PTEROYLGLUTAMIC ACID

- Angier, R. B., et al.: Synthesis of a compound identical with the *L. casei* factor isolated from liver, *Science* 102:227, 1945.
- Angier, R. B., et al.: The structure and synthesis of the liver *L. casei* factor, *Science* 103:667, 1946.
- Berry, L. J., and T. D. Spies: The present status of folic acid, *Blood* 1:271, 1946.
- Doan, C. A.: Folic acid (synthetic *L. casei* factor) an essential panhematopoietic stimulus—experimental and clinical studies, *Am. J. M. Sc.* 212:257, 1946.
- Mitchell, H. K., E. E. Snell and R. J. Williams: The concentration of "folic acid," *J. Am. Chem. Soc.* 63:2284, 1941.
- Spies, T. D., W. B. Frommeyer, Jr., C. F. Vilter and A. English: Anti-anemic properties of thymine, *Blood* 1:185, 1946.
- Stokstad, E. L. R.: Some properties of a growth factor for *Lactobacillus casei*, *J. Biol. Chem.* 149:573, 1943.

#### RADIOACTIVE PHOSPHORUS

- Erf, L. A.: Radiophosphorus as the treatment of choice in primary polycythemia, *Am. J. M. Sc.* 1:363, 1946.
- Hempelmann, Jr., L. A., E. H. Reinhard, C. V. Moore, O. S. Bierbaum and S. Moore: Hematologic complications of therapy with radioactive phosphorus, *J. Lab. & Clin. Med.* 29:1020, 1944.

- Lawrence, J. H., K. G. Scott and L. W. Tuttle: Studies on leukemia with the aid of radioactive phosphorus, *New Internat. Clinics* 3: 33, 1939.
- Reinhard, E. H., C. V. Moore, O. S. Bierbaum and S. Moore: Radioactive phosphorus as a therapeutic agent; A review of the literature and analysis of the results of treatment of 155 patients with various blood dyscrasias, lymphomas and other neoplastic diseases, *J. Lab. & Clin. Med.* 31: 107, 1946.
- Warren, S.: The therapeutic use of radioactive phosphorus, *Am. J. M. Sc.* 209: 701, 1945.
- Warren, S.: Availability of radioactive isotopes—an announcement from headquarters, Manhattan project, Washington, D. C., *Science* 103: 697, 1946.

#### NITROGEN MUSTARDS

- Gilman, A., and F. S. Phillips: The biological actions and therapeutic applications of the B-chloroethyl amines and sulfides, *Science* 103: 409, 1946.
- Goodman, L. S., M. W. Wintrobe, W. Dameshek, M. J. Goodman, A. Gilman and M. T. McLennan: Nitrogen mustard therapy—use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders, *J. A.M.A.* 132: 126, 1946.
- Jacobson, L. O., C. L. Spurr, E. S. Guzman Barron, T. Smith, C. Lushbaugh and G. F. Dick: Nitrogen mustard therapy; studies on the effect of methyl-bis (beta-chloroethyl) amine hydrochloride on neoplastic diseases and allied disorders of the hemopoietic system, *J. A.M.A.* 132: 263, 1946.
- Rhoads, C. P.: Nitrogen mustards in the treatment of neoplastic disease, *J. A.M.A.* 131: 656, 1946.

#### PHENYLHYDRAZINE

- Griffin, H. Z., and E. V. Allen: The control and complete remission of polycythemia vera following the prolonged administration of phenylhydrazine hydrochloride, *Am. J. M. Sc.* 185: 1, 1933.

Griffin, H. Z., and H. M. Conner: The untoward effects of treatment by phenylhydrazine hydrochloride, J.A. M.A. 92:1505, 1929.

Stealy, C. L., and H. S. Sumerlin: Polycythemia vera, final report on a case under continual treatment with phenylhydrazine hydrochloride for eleven years, J.A. M.A. 126:954, 1926.

#### URETHANE

Paterson, E., A. Haddow, I. A. Thomas and J. M. Watkinson: Leukaemia treated with urethane compared with deep x-ray therapy, Lancet 1:677, 1946.

#### ARSENIC

Kandel, E. V., and G. V. LeRoy: Chronic arsenical poisoning during the treatment of chronic myeloid leukemia, Arch. Int. Med. 60:846, 1937.

#### ANTICOAGULANTS

Allen, J. G., and L. O. Jacobson: Hyperheparinemia: cause of the hemorrhagic syndrome associated with total body exposure to ionizing radiation, Science 105:388, 1947.

Barker, N. W., H. E. Cromer, M. Hurn and J. M. Waugh: The use of dicumarol in the prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration, Surgery 17:207, 1945.

Bauer, G.: Heparin therapy in acute deep venous thrombosis, J.A.M.A. 131:196, 1946.

Evans, J. A., and R. J. Boller: The subcutaneous use of heparin in anticoagulation therapy, J.A.M.A. 131:879, 1946.

Jorpes, J. E.: Heparin in the Treatment of Thrombosis, New York, Oxford, 1947.

Link, K. P.: The anticoagulant 3, 3-methylenebis (4-hydroxycoumarin), Federation Proc. 4:176, 1945.

Loewe, L., and P. Rosenblatt: A new practical method for subcutaneous administration of heparin—preliminary report, Am. J. M. Sc. 208:54, 1944.

Peters, H. R., J. R. Guyther and C. E. Brambel: Dicumarol in acute coronary thrombosis, J.A.M.A. 130:398, 1946.

Quick, A. J.: The anticoagulants effective in vivo with special reference to heparin and dicumarol, *Physiol. Rev.* 24:297, 1944.  
Rosenbloom, D., and J. J. Crane: Massive hematuria due to dicumarol overdosage, *J.A.M.A.* 132:924, 1946.

## COAGULANTS

Cromer, H. E., and N. W. Barker: The effect of large doses of menadione bisulfite (synthetic vitamin K) on excessive hypoprothrombinemia induced by dicumarol, *Proc. Staff Meetings, Mayo Clinic* 19:217, 1944.  
Potter, E. L.: The effect on infant mortality of vitamin K administered during labor, *Am. J. Obst. & Gynec.* 50:235, 1945.  
Richards, R. K., and S. Shapiro: Experimental and clinical studies on the action of high doses of hykinone and other menadione derivatives, *J. Pharmacol. & Exper. Therap.* 84:93, 1945.

# Drugs Affecting the Gastro-Intestinal Tract

INTRODUCTION

ANTACIDS

CHOLERETICS

CATHARTICS

ANTIDIARRHEAL AGENTS

MISCELLANEOUS PREPARATIONS

PREPARATIONS

## INTRODUCTION

Drugs discussed in this chapter include antacids, chol-  
eretics, cathartics, antidiarrheal agents and miscellaneous  
preparations which are either little used or whose thera-  
peutic value has not been fully established. Other drugs  
often administered for their effect on the gastro-intestinal  
tract include opium and morphine, used to treat diarrhea  
and to relieve severe abdominal pain; antispasmodics such  
as papaverine, the parasympatholytic agents and the ali-  
phatic amine, octin, which are used in the treatment of  
gastro-intestinal and biliary spasm; posterior pituitary,  
used to stimulate the intestinal musculature and to allay  
distention; and the anthelmintics, amebacides and certain  
sulfonamides which are used in infections of the gastro-in-  
testinal tract.

## ANTACIDS

Antacids are drugs which reduce the acidity of the gas-  
tric secretion. They are used chiefly in the treatment of  
peptic ulcer. While the etiology of this condition is not

fully understood, it is generally believed to be due to the irritant and digestive action of hydrochloric acid and probably also of pepsin on a susceptible area of the gastric mucosa. This view has been supported recently by Dragstedt and his associates, who have reported striking improvement in patients with chronic refractory ulcers following section of the vagus. The results to date indicate that the operation leads to reduced secretion and motility, relief of pain and healing of the ulcer.

Antacids either act by a direct neutralization of the hydrochloric acid of the stomach or by adsorption of excess hydrogen ions leading to a higher pH and a resultant decrease in peptic activity. Included in the first group are sodium bicarbonate, magnesium oxide, tribasic calcium carbonate, calcium carbonate and magnesium carbonate. Calcium carbonate is one of the most widely used preparations because of its cheapness and its non-purgative action. Excessive use of soluble, absorbable preparations such as sodium bicarbonate may lead to systemic alkalosis.

Adsorbent preparations are colloidal in nature and include aluminum hydroxide, aluminum silicate, colloidal magnesium silicate and aluminum phosphate gel. These substances are also said to have a protective, lining action on the mucosa which may relieve the pain and promote healing of the ulcerated area. The colloidal preparations tend to have a constipating effect and should therefore be supplemented by noncolloidal magnesium preparations which have a laxative action in adequate dosages. The colloidal preparations may also interfere with the absorption from the gastro-intestinal tract and, with the exception of aluminum phosphate, may lead to a depletion in phosphorus from the bones due to the combination in the intestinal tract of aluminum and phosphorus.

Gastric mucin has been used to a limited extent in the treatment of gastric ulcer. Its activity may be due to a protective coating action or to an absorbent action.



Detergents such as sodium alkyl sulfate and sodium lauryl sulfate inactivate pepsin in vitro but their action in vivo is disappointing. These preparations have not as yet proved of value in the treatment of gastric ulcer.

### CHOLERETICS

Choleretics are substances which increase the output of bile. The most important are bile salts and related preparations.

The bile salts when given by mouth are absorbed from the intestine and re-excreted by the liver in the bile, thus entering the same cyclic process as endogenous bile salts. They are of value in promoting the absorption of fats and fat-soluble vitamins from the intestinal tract when the normal biliary output is reduced or absent.

Dehydrocholic acid (decholin), an oxidation product of cholic acid derived from natural bile salts, and its sodium salt, sodium dehydrocholate, have a *hydrocholeretic* action. They increase the volume of the biliary secretion by increasing the water content without increasing the output of the bile salts. These preparations are of some value in "flushing out" the biliary tract but should be avoided in cases of complete biliary obstruction. They have a mild diuretic action and potentiate the action of mercurial diuretics. These preparations may be employed in cholecystography to hasten the appearance of the shadow and the subsequent removal of the dyestuff from the biliary tract.

Cholecystagogues are substances which cause evacuation of the gallbladder, either by the contraction of its musculature (fats and cholecystokinin) or by relaxation of the sphincter of Oddi (nitrites and antispasmodics).

### CATHARTICS

Cathartics are used to relieve constipation or to hasten the evacuation of toxic substances from the bowel. Cathartic action depends usually on increased intestinal movements induced either by increased bulk of the intestinal

contents or by irritation of the intestinal musculature. Cathartic drugs vary considerably in the degree to which they act and are sometimes classified in approximate order of increasing activity as aperients, laxatives, cathartics, eccoprotics, purgatives, physics, hydragogues and drastics. They are more conveniently classified according to their method of action or their chemical nature.

Cathartics have been exploited by the patent-medicine industry probably more than any other group of drugs, and many cases of chronic constipation and of bowel irritation have resulted from their indiscriminate use. Indications for their use include the elimination of poisons, the medical induction of labor, the presence of painfully hard stools, the presence of certain anorectal lesions, during late pregnancy and early puerperium, and to prevent straining at stool in extreme hypertension, aneurysm, abdominal hernia or recent coronary occlusion. The use of cathartics to relieve gastro-intestinal symptoms of unknown cause cannot be too emphatically condemned.

*Drugs which act by increasing the bulk of the gastrointestinal contents:*

1. Saline cathartics consist of poorly absorbable salts that hold water in the gut by osmotic force, thus increasing the bulk and fluidity of the intestinal contents. They include sodium, magnesium and potassium sulfates, citrates, tartrates and phosphates. If given in hypertonie solution, these salts draw water from the body tissues, hence their cathartic action is slower and tissue dehydration may occur. The latter effect may, however, be of value in edema. Isotonic solutions are less irritating to the stomach and are passed more rapidly through the pyloric sphincter than hypertonic solutions. The palatability of the saline cathartics may be improved by prescribing them in the form of effervescent preparations.

Occasional cases of magnesium poisoning have been reported due to unusual absorption of magnesium sulfate. The

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4. Miscellaneous irritants include phenolphthalein and mercurous chloride (calomel). Phenolphthalein is frequently included in proprietary cathartics because of its tastelessness and its low toxicity. It may cause a skin rash in sensitive individuals. Mercurous chloride should be followed by another cathartic if effective results are not obtained following its administration since the insoluble mercurous ion may be changed in the intestine to the soluble mercuric ion and lead to symptoms of mercury poisoning (mercurialism), such as salivation, stomatitis and nephritis.

### ANTIDIARRHEAL AGENTS

Nonspecific agents used in the treatment of diarrhea include adsorbents, such as activated charcoal, bentonite and kaolin, or substances such as bismuth subnitrate or subcarbonate, which are thought to form a protective coating over the mucous membrane of the intestinal tract. Bismuth subnitrate is occasionally decomposed in the intestine with the formation of the more toxic nitrite. Adsorbents are of value in the treatment of poisoning by mercuric chloride and alkaloïds. Huge quantities are necessary for effective results, and with kaolin preparations partial or complete intestinal obstruction may occur.

### MISCELLANEOUS PREPARATIONS

Emetics are drugs which produce vomiting. In small doses they act as expectorants, increasing the secretion of fluid from the respiratory tract. Emetics act either locally by irritating the stomach or centrally by stimulating the vomiting center in the medulla. The locally acting emetics include zinc sulfate, copper sulfate, alum and mustard. Centrally acting emetics include ipecac, antimony and potassium tartrate (tartar emetic) and apomorphine. Most emetics are irritating to the stomach and if not effective promptly must be removed by stomach pump. Furthermore, emesis in a semiconscious patient may lead to

characteristic symptom is profound depression. Calcium salts are effective antidotes.

2. Plant colloids include insoluble gums, such as plantago seed (psyllium seed) and agar, which take up water and swell to give considerable bulk, and bran, which contains a high proportion of indigestible celluloses and hemicelluloses which have a water-binding action. Bran may also act by irritating the mucous membrane of the intestinal tract and should not be used in such conditions as colitis.

3. Emollients include bland oils, such as liquid petrolatum and olive oil. It has been suggested that these substances coat the intestine with an oily film which interferes with the absorption of water and thus increases the bulk and fluidity of the intestinal contents. Prolonged use of liquid petrolatum may lead to the loss of the fat-soluble vitamins, to loss of weight due to poor absorption of food-stuffs from the intestinal tract and to pruritus and due to an interference with anal hygiene by leakage of oil from the anus.

#### Drugs which act by irritation or stimulation:

1. Irritant oils include castor oil and croton oil. The activity of castor oil is due to its hydrolysis in the intestine to the mildly irritating ricinoleic acid. Croton oil contains a violently irritating resin and is seldom used except in veterinary medicine.

2. Anthracene cathartics, such as senna, rhubarb, cascara and aloe, owe their activity to polyhydroxyanthraquinones, present usually as glycosides. Such preparations were formerly thought to have a tonic effect on the intestinal musculature.

3. Cathartic resins include such preparations as euphorbium, jalap, ipomoea, elaterin, podophyllum, gamboge and colocynth in which the active ingredient is often a glucoside. These substances are seldom used nowadays because of the severity of their action.

4. Miscellaneous irritants include phenolphthalein and mercurous chloride (calomel). Phenolphthalein is frequently included in proprietary cathartics because of its tastelessness and its low toxicity. It may cause a skin rash in sensitive individuals. Mercurous chloride should be followed by another cathartic if effective results are not obtained following its administration since the insoluble mercurous ion may be changed in the intestine to the soluble mercuric ion and lead to symptoms of mercury poisoning (mercurialism), such as salivation, stomatitis and nephritis.

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entrance of vomitus into the respiratory tract. Hence the tendency is to replace emetics in modern practice by the stomach pump. Apomorphine, which is prepared from morphine by the abstraction of one molecule of water, is probably one of the safest and most effective emetics. Given by hypodermic injection, it acts promptly in very small dosage and is nonirritating to the stomach.

In small doses, emetics increase sweating (diaphoretic action) and increase the secretion of fluid from the respiratory tract (expectorant action). Expectorants are of value in the treatment of inflammatory conditions of the lungs and of the air passages by aiding in the removal of mucus or exudates. Other types of expectorants include saline expectorants, such as ammonium chloride or carbonate, citrates and iodides, and irritant expectorants, such as terpin hydrate, cresote and squill, which are said to stimulate repair processes by irritation of the mucous membrane.

Carminatives are substances which relieve gaseous distension of the stomach or intestines. They include sodium bicarbonate and a number of flavoring agents, such as caraway, capsicum, cardamon, cinnamon, clove, ginger and peppermint, in which the active agent is a volatile oil.

Bitters are substances used to increase salivary and gastric secretions and to improve the appetite. Their action is probably largely psychic, although they may act reflexly by stimulating the taste buds. They are effective in very small doses. Preparations include compound tincture of gentian, tincture of nux vomica, and quinine and its salts. They are rarely prescribed in modern practice.

Hydrochloric acid in dilute solution may be prescribed when the normal hydrochloric acid of the stomach is reduced or absent. Its effectiveness is probably due to its action in liberating gastro-intestinal hormones, rather than to any effect on the free acidity of the gastric juice.

Pancreatin is a preparation containing the enzymes trypsin, amylase and lipase. It is obtained from the fresh

pancreas of cattle and hogs. It is used both in the preparation of predigested foodstuffs and in the treatment of digestive disorders, especially in patients in which the normal pancreatic secretion is deficient.

Gastro-intestinal Hormones. The control of the digestive processes appears to be due at least in part to humeral agents liberated from the mucosa of the intestinal tract by the stimulus of eating. A number of active preparations have been prepared and studied, some of which show promise as therapeutic agents.

Enterogastrene is a partially purified preparation obtained from the upper intestine which inhibits gastric secretion and motility. Ivy and his associates have shown that enterogastrene has a protective action against experimental ulcers in dogs and have reported encouraging preliminary clinical results in the treatment of peptic ulcer in man.

Secretin is the humeral agent responsible for stimulating the flow of pancreatic juice. It is liberated from the inactive prosecretin by the action of hydrochloric acid in the upper duodenum. It has limited value in the diagnosis of pancreatic disease. It is effective only on intravenous injection. Cholecystokinen is an agent obtained from intestinal extracts which produces evacuation of the gallbladder by causing it to contract. It may prove of diagnostic value in gallbladder disease.

## PREPARATIONS

### ANTACIDS

Magnesia magma (milk of magnesia) U.S.P. Mixture of magnesium hydroxide B.P. Approximately 8 per cent solution of magnesium hydroxide. Antacid, 4 cc. Laxative, 15 cc.

Magnesium carbonate U.S.P.; B. P. Antacid, 0.6 Gm. Laxative, 8.0 Gm.

Magnesium oxide (light and heavy) U.S.P.; B.P. Antacid, 0.25 Gm. Laxative, 4.0 Gm.



Magnesium trisilicate U.S.P.; B. P. 1.0 Gm.

Tribasic calcium phosphate N.N.R. Calcium phosphate B.P.  
1-5 Gm.

Tribasic magnesium phosphate N.N.R. 1-5 Gm.

Dried aluminum hydroxide gel U.S.P. 0.6 Gm.

Aluminum hydroxide gel U.S.P. Contains approximately  
4 per cent  $\text{Al}_2\text{O}_3$ , chiefly as hydrous oxide of aluminum.  
8 cc.

Aluminum phosphate gel N.N.R. 15-30 cc.

Gastric mucin N.N.R. 2.5 Gm.

#### CHOLERETICS

Ox-bile extract U.S.P.; B.P. 0.3 Gm.

Ox-bile extract tablets U.S.P. Usually contain 0.3 Gm.  
extract of ox bile.

Dehydrocholic acid N.N.R. 0.25-0.5 Gm.

Sodium dehydrocholate N.N.R. Available as a 20 per cent  
solution for intravenous injection. 5-10 cc.

#### CATHARTICS

Magnesium sulfate (Epsom salt) U.S.P.; B.P. 15 Gm.

Magnesium citrate solution U.S.P. Contains about 1.6 per  
cent magnesium citrate in flavored carbonate solution.  
200 cc.

Compound effervescent powders (Seidlitz powders) U.S.P.  
Blue paper contains 2.5 Gm. sodium bicarbonate and 7.5  
Gm. potassium and sodium tartrate; white paper contains  
2.16 Gm. tartaric acid.

Sodium phosphate U.S.P. B.P. 4 Gm.

Effervescent sodium phosphate U.S.P. Contains 20 per cent  
sodium phosphate. B.P. Contains 50 per cent sodium  
phosphate.

Sodium biphosphate U.S.P.; B.P. 0.6 Gm.-4.0 Gm.

Sodium sulfate (Glauber's salt) U.S.P.; B. P. 15 Gm.

Effervescent sodium sulfate B.P. Contains 50 per cent so-  
dium sulfate.

Agar B.P.; U.S.P. Dried mucilaginous substance extracted from various species of Gelidium and closely related algae. 4 Gm.

Plantago seed (psyllium seed) N.N.R. Dried seed from various species of plantago. 4-15 Gm.

Metamucil N.N.R. Contains approximately 50 per cent powdered psyllium seed. 4-7 Gm.

Liquid petrolatum U.S.P.; liquid paraffin B.P. 15 cc. Liquid petrolatum emulsion U.S.P. Contains 50 per cent liquid petrolatum.

Olive oil U.S.P.; B.P. 30 cc. Castor oil U.S.P.; B.P. Oil from seeds of *Ricinus communis*. 15 cc.

Senna U.S.P.; B.P. Dried leaflets of *Cassia acutifolia* or *C. angustifolia*. 2.0 Gm.

Senna pod B.P. Used for preparing fluid extract of senna. 2.0 Gm.

Senna fluid extract U.S.P.; B. P. 1 cc. represents 1 Gm. senna.

Senna syrup U.S.P.; B.P. Contains 25 per cent fluid extract of senna. 8 cc.

Confection of senna B.P. Contains 10 per cent senna. 4-8 Gm.

Concentrated infusion of senna B.P. Contains 80 per cent senna pod. 2-8 cc.

Fresh infusion of senna B.P. Contains 10 per cent senna pod. 15-60 cc.

Compound mixture of senna (black draught) B.P. 30-60 cc. Rhubarb U.S.P.; B.P. Dried roots and rhizome of various species of rheum. 1 Gm.

Compound powder of rhubarb B.P. (Gregory's powder). Contains 25 per cent rhubarb with light and heavy magnesium carbonate. 0.6-4 Gm.

Compound rhubarb pill B.P. Contains 25 per cent rhubarb with aloe, myrrh, hard soap and flavoring matter. 0.25-0.5 Gm.

Aromatic rhubarb tincture U.S.P. Contains 20 per cent rhubarb.

Aromatic rhubarb syrup U.S.P. Contains 15 per cent aromatic tincture of rhubarb. 10 cc.

Compound tincture of rhubarb B.P. Contains 10 per cent rhubarb. 2-4 cc.

Cascara sagrada fluid extract U.S.P.; B.P. 1 cc. represents 1 Gm. cascara sagrada. 1-4 cc.

Aromatic cascara sagrada fluid extract U.S.P. Elixir of cascara sagrada B.P. 1 cc. represents 1 Gm. cascara sagrada. 2 cc.

Cascara sagrada extract U.S.P. 1 Gm. of extract represents 3 Gm. cascara sagrada. 0.3 Gm.

Cascara sagrada extract tablets U.S.P. Usually contain 0.12, 0.2 and 0.3 Gm.

Dry extract of cascara sagrada B.P. 0.12-0.5 Gm.

Aloe U.S.P.; B.P. Dried juice of leaves of various species of aloe. 0.25 Gm.

Aloin U.S.P.; B.P. Mixture of active principles of aloe. 15 mg.

Pill of aloes B.P. Contains 58 per cent aloe. 0.25-0.5 Gm.

Pill of aloes and asefetida B.P. Contains 30 per cent aloe. 0.25-0.5 Gm.

Pill of aloes and iron B.P. Contains 20 per cent aloe. 0.25-0.5 Gm.

Jalap B.P. Dried tubercles of *Ipomoea purga*.

Powdered jalap B.P. 0.3-1.2 Gm.

Compound powder of jalap B.P. Contains 30 per cent powdered jalap. 0.6-4 Gm.

Ipomoea B.P. Dried root of *Ipomoea orizabensis*. 0.3-1.2 Gm.

Scammony resin B.P. Mixture of resins from ipomoea. 0.03-0.2 Gm.

Podophyllum B.P. Dried rhizome and roots of *P. peltatus*. 0.12-0.6 Gm.

Indian podophyllum B.P. Dried rhizome and roots of *P. emodi*. 0.12-0.6 Gm.

Resin of podophyllum B.P. Mixture or resin obtained from *P. pellatus* or *P. emodi*. 15-60 mg.

Colocynth B.P. Dried pulp of fruit of *Citrullus colocynthis*. 0.12-0.3 Gm.

Compound extract of colocynth B.P. Contains colocynth, aloes, scammony resin, curd soap and cardamon. 0.12-0.5 Gm.

Pill of colocynth and hyoscyamus B.P. Contains colocynth (12.5 per cent), aloes (25 per cent), scammony resin (25 per cent), dry extract of hyoscyamus (12.5 per cent), curd soap, oil of clove and glucose solution. 0.25-0.5 Gm. Phenophthalein U.S.P.; B. P. 0.06 Gm.

# ANTIDIARRHEAL AGENTS

Activated charcoal U.S.P.

Kaolin B.P. Native aluminum silicate. 15-60 Gm.

Bentonite U.S.P. Native, colloidal, hydrated aluminum silicate.

Bentonite magma U.S.P. Contains 5 per cent bentonite. Bismuth subcarbonate U.S.P.; B.P. 1 Gm.

# MISCELLANEOUS AGENTS

Zinc sulfate U.S.P.; B.P. 0.65-2.0 Gm.

Cupric sulfate U.S.P.; B.P. 0.3 Gm.

Alum U.S.P.; B.P. Either potassium aluminum sulfate or ammonium aluminum sulfate. Astringent, 0.3-1 Gm. Emetic, 2-4 Gm.

Black mustard U.S.P. Dried seeds of various species of brassica. 10 Gm.

Ipecac (nauha) U.S.P.; B.P. Dried rhizome and roots of *Cephaelis ipecacuanha* or *C. acuminata*. Yields not less than 2 per cent of water-soluble alkaloids of ipecac. 0.5 Gm.

- Ipecac fluid extract U.S.P.; B.P. Contains approximately 2 per cent ether-soluble alkaloids of ipecac. 0.5 cc.  
Ipecac syrup U.S.P. Contains 7 per cent fluid extract of ipecac. Emetic, 8 cc. Expectorant, 1-2 cc.  
Antimony potassium tartrate (tartar emetic) U.S.P.; B.P. Emetic, 30 mg. Expectorant, 3 mg.  
Apomorphine hydrochloride U.S.P.; B.P. Emetic, 5 mg. Expectorant, 1 mg.  
Anise oil U.S.P. 0.2-0.3 cc.  
Caraway U.S.P.; B.P. 0.6-2 Gm.  
Cardamom seed U.S.P.; B.P. 0.6-2 Gm.  
Compound cardamom tincture U.S.P.; B.P. Contains cardamom seed, cinnamon and caraway. 4 cc.  
Cinnamon U.S.P.; B.P. 0.3-1.2 Gm.  
Cinnamon oil U.S.P.; B.P. 0.1 cc.  
Clove U.S.P.; B.P. 0.32-0.65 Gm.  
Ginger U.S.P.; B.P. 0.6 Gm.  
Ginger fluid extract U.S.P. 0.6 cc.  
Peppermint U.S.P.  
Peppermint oil U.S.P. 0.06-0.3 cc.  
Compound gentian tincture U.S.P.; B.P. Contains gentian, bitter orange peel and cardamom seed. 4 cc.  
Tincture of nux vomica B.P. 0.6-2 cc.  
Diluted hydrochloric acid U.S.P.; B.P. Contains approximately 10 per cent hydrochloric acid. 4 cc. (well diluted).  
Pancreatin U.S.P.; B.P. 0.5 Gm.

## BIBLIOGRAPHY

### ANTACIDS

- Collins, E. N.: Use of aluminum hydroxide and other nonabsorbable antacids in treatment of peptic ulcer, J.A.M.A. 127:899, 1945.  
Ehrmann, R.: Drugs in the treatment of peptic ulcer and hypersecretion, Am. J. Digest. Dis. 12:154, 1945.  
Kirsner, J. B., and R. A. Wolff: The effect of sodium alkyl sulfate on the peptic activity

tents and on the healing of gastric ulcer in man, Gastroenterology 2: 93, 1944.

Nelson, E. E.: Gastric antacids, Internat. M. Digest 40: 376, 1942.

Steigmann, F., and A. R. Marks: Inhibition of peptic activity in the treatment of peptic ulcer, Am. J. Digest. Dis. 11: 173, 1944.

Thornton, T. F., Jr., E. H. Storer and L. R. Dragstedt: Supradaphragmatic section of the vagus nerves—effect on gastric secretion and motility in patients with peptic ulcer, J.A.M.A. 130: 764, 1946.

CHOLERETICS

Ivy, A. C.: Cholecystagogues, choleretics and cholepoetics, Gastroenterology 3: 54, 1944.

CATHARTICS

Betha, O. W.: The use of cathartics, J.A.M.A. 107: 1298, 1936.

Fantus, B.: Useful Cathartics, Chicago, A. M. A., 1927.

Gray, H., and M. L. Tainter: Colloid laxatives available for clinical use, Am. J. Digest. Dis. 8: 130, 1941.

Micks, R. H.: Modern therapeutics. IX—the use and abuse of aperients, Practitioner 144: 285, 1940.

Morgan, J. W.: The harmful effects of mineral oil (liquid petrolatum) purgatives, J.A.M.A. 117: 1335, 1941.

Nelson, E. E.: The treatment of constipation, Internat. M. Digest 42: 308, 1943.

ANTIDIARRHEAL AGENTS

Miller, G. E.: Bismuth subnitrate poisoning with methemoglobinemia, Gastroenterology 4: 430, 1945.

Emery, Jr., E. S.: The use of adsorbents in gastro-intestinal diseases, J.A.M.A. 108: 202, 1937.

MISCELLANEOUS PREPARATIONS

Brown, C. L.: The use of expectorants, J.A.M.A. 109: 268, 1937.

Carlson, A. J., J. Van de Erve, J. H. Lewis and S. J. Orr: Contributions to the physiology of the stomach; XVI.

The action of the so-called stomachics or bitters on the hunger mechanism, *J. Pharmacol. & Exper. Therap.* 6:209, 1914.

Frankel, E.: Hydrochloric acid therapy in achlorhydria, *Am. J. Digest. Dis.* 12:15, 1945.

Ivy, A. C.: *Internal Secretions of the Gastro-intestinal Tract—Glandular Physiology and Therapy*, Chicago, A. M. A., 1942.

Ivy, A. C.: The prevention of recurrence of "peptic" ulcer—an experimental study, *Gastroenterology* 3:443, 1944.

Van Liere, E. J., and D. W. Northup: The effect of carminatives on the emptying time of the normal human stomach, *J. Pharmacol. & Exper. Therap.* 76:39, 1942.

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Oxytocics are occasionally used for the temporary relief of excessive uterine bleeding in the nonpregnant patient or to hasten or complete therapeutic abortions. In cesarean sections, posterior pituitary extracts or ergonovine injected into the uterine musculature causes a shrinkage of the musculature that facilitates surgery and decreases bleeding. Oxytocics are rarely successful as abortifacients in early pregnancy, though they are frequently used illegally for this purpose.

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## INTRODUCTION

### PREPARATIONS

#### ABORTIFACIENTS

#### MISCELLANEOUS OXYTICS

#### QUININE

#### POSTERIOR PITUITARY

#### ERGOT

#### INTRODUCTION

# Oxytocics



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far exceeding those of its therapeutic use. In contrast to ergotamine, ergonovine in therapeutic doses does not cause an elevation of the blood pressure. It can be given by mouth, intramuscularly or intravenously. It has a prompt oxytocic effect even when given by mouth in contrast with that of ergotamine, whose onset of action is too slow for use in emergencies.

Some authorities question the advisability of giving oxytocics before the placenta is delivered in case hourglass contractions are produced, necessitating manual removal of the placenta and increasing the danger of puerperal fever. In hospital practice, however, the danger of such complications is minimal and it is customary in the Chicago Lying-in Hospital to inject 0.2 mg. of ergonovine intravenously as soon as the head is delivered. A prompt contraction of the uterus follows, which assists in the separation and delivery of the placenta, reducing the duration of the third stage of labor and decreasing the blood loss by as much as 75 per cent. The effect of this dose will last from 4 to 6 hours, following which postpartum bleeding can be controlled with further doses of ergonovine, ergotamine or liquid extract of ergot. Use of ergot preparations in the puerperium is also said to hasten involution of the uterus, reduce lochial secretions and limit the spread of uterine infections, though Moir, in a recent review, has questioned the efficacy of the drug in these respects.

Recently, Stoll and his associates have synthesized a lysergic-acid derivative, methergine. Like ergonovine, methergine has an oxytocic effect but little or no sympatholytic effect. This compound is of interest because of the possibility of replacing the limited supply of ergonovine by a synthetic substitute.

Use of Ergotamine in Migraine. Ergotamine tartrate (gynergen) usually provides prompt relief in many cases of migraine. It has been suggested that the pain of migraine is associated either with spasm or with dilation of

## ERGOT

Ergot is a fungus, *Claviceps purpurea*, which infects various grains. The official (N.F.) source of ergot is the dried sclerotium of the fungus developed on rye plants. A number of alkaloids have been isolated from ergot, all of which have lysergic acid as a basic nucleus. The most important of these alkaloids are the levorotatory compounds ergotoxine (1906), ergotamine (1918), ergonovine (1935) and ergosine (1936) and their respective dextrorotatory isomers, ergotinine (1878), ergotamine (1920), ergometrinine (1935) and ergosinine (1936). The levorotatory compounds have marked pharmacologic activity while the dextrorotatory compounds are relatively inert. Recent work by Stoll and his associates indicates that ergotoxine is not a pure compound but a mixture of ergokryptine, ergocornine and ergocristine in varying amounts.

The ergot alkaloids have the common property of stimulating smooth muscle directly. Ergotoxine and ergotamine also have a sympatholytic effect when used in large doses. This action is limited to excitatory effects of sympathin or epinephrine.

For many years, it was believed that all the oxytocic activity of ergot was vested in the water-insoluble alkaloids, ergotoxine and ergotamine. However, in 1932, Moir showed that aqueous extracts of ergot had a definite uterus-stimulating effect when given by mouth, and by 1935 four laboratories working independently succeeded in isolating from such extracts an alkaloid known officially in the United States as *ergonovine*, and in Britain as *ergometrine*. Ergotamine and ergotoxine have very similar pharmacologic and toxicologic properties, though the latter has had little clinical use, since it appears to be a somewhat more toxic and a less reliable uterine stimulants. Ergotamine is usually given by intramuscular injection since it is erratically absorbed when given by mouth. Ergonovine has fewer side reactions than ergotamine or ergotoxine and it is nontoxic in doses

carried along in the extraction process. The most commonly used method for the bioassay of ergot compares the ability of the unknown preparation to cause darkening of the cock's comb with that of a solution of ergotoxine ethanesulfonate. All the pharmacologically active alkaloids are measured by this method. The Clark-Broom method is based on the antagonism of the stimulant effect of epinephrine on the isolated rabbit uterus. This method determines only alkaloids with a sympatholytic effect, such as ergotoxine and ergotamine, and is therefore not applicable to ergonovine.

## POSTERIOR PITUITARY

The value of posterior-pituitary extracts in obstetrics was first demonstrated by Blair Bell in 1909 and by Hofbauer in 1911, following the discovery by Dale in 1906 of the direct stimulating action of posterior-pituitary extracts on the isolated uterus. In 1928, Kamm and his associates were able to separate an oxytocic fraction (pitocin) and a pressor fraction (pitressin) from posterior-pituitary extracts (pituitrin) (see Chapter 21).

There is much experimental evidence to indicate that the response of uterine smooth muscle to posterior pituitary and its various fractions depends upon the species of animals, the phase of the menstrual or estrus cycle, whether the uterus is gravid or nongravid, the stage of pregnancy and whether observations are made on the uterus in situ or on strips of uterine muscle suspended in a saline bath. In brief, the nonpregnant human uterus in situ responds to posterior-pituitary extracts, and especially to the pressor fraction, at all stages of the menstrual cycle, the response being somewhat exaggerated just before and during menstruation. In early pregnancy the uterus is comparatively unreactive to posterior pituitary and to the separate principles. In late pregnancy and during parturition and the early puerperium, the uterus is very sensitive to the oxytocic fraction of the pituitary extracts, becoming

the vessels of the scalp and the dura mater and that ergotamine gives relief in the latter instance by producing vasoconstriction. Ergonovine is much less effective in this respect. A new compound, dihydroergotamine (D.H.E. 45), formed by the hydrogenation of ergotamine, has recently been reported to be as effective as ergotamine in the treatment of migraine. It has little or no uterus-stimulating activity and is much less toxic than ergotamine.

**Ergot Poisoning.** Ergot poisoning (ergotism) may result from the injudicious clinical use of ergot preparations or from the ingestion of ergot-infested rye. Epidemics of ergotism from the latter cause were formerly quite common, especially in European countries. Two types of chronic ergotism are differentiated, the gangrenous type and the spasmodic convulsive type. The gangrenous type, which is due to vascular spasm, is characterized by severe pain and cyanosis in the extremities, which may be followed by dry gangrene. In the Middle Ages this type of poisoning was known as the "fire of St. Anthony" or "holy fire." In the convulsive type of ergotism, twitchings and epileptiform convulsions occur, frequently followed by delirium, blindness, deafness, paralysis and insanity. Since this type of poisoning is not observed in communities in which the diet is rich in dairy products, it has been suggested that it is associated with a vitamin A deficiency.

Ergot preparations should be used cautiously, especially if repeated administration is necessary, because of the danger of causing gangrene. The treatment, should this occur, is not very satisfactory though it has been claimed that relief may be afforded by the vascular antispasmodic action of papaverine. Ergonovine is apparently free from the gangrene-producing action of ergotamine and ergotoxine.

**Standardization of Ergot.** Crude ergot preparations are assayed either by biologic or chemical procedures. The chemical methods in general tend to give values that are too high because of the fact that inactive alkaloids may be

Calcium has been shown to be essential for uterine contractions, and the administration of calcium preparations, either alone or with an oxytocic, has been reported as being these drugs.

There is some evidence that *estrogens* increase the mobility of the uterine musculature. Clinical results are not very encouraging, probably because the effect is slow, no changes being evident for 24 hours or more. There is some evidence that the preliminary administration of estrogens sensitizes the uterus to ergot or pituitary, causing them to be more effective in producing therapeutic abortions early in pregnancy when the uterus is normally refractory to these drugs.

## MISCELLANEOUS OXYTOCICS

Quinine, especially in combination with castor oil, has long been popular for the induction of labor. Its oxytocic effect is unreliable and probably only in about half of the cases does it actually stimulate uterine contractions. Furthermore, quinine may pass through the placental barrier and cause toxic effects in the fetus; cases of death, blindness or deafness have been reported. Occasionally, too, the mother may have an idiosyncrasy to quinine or display evidences of cinchonism. Danger of toxic symptoms is minimized if the dose is limited to 0.6 Gm. and restricted to patients at or beyond term. More effective contractions may be obtained by following the quinine with small doses of posterior pituitary.

## QUININE

(pituitary) and solution of posterior-pituitary sulfonate have all had clinical trials. The first two preparations are probably without virtue. While the clinical reports on pituitary are not extensive, it does appear to have an increased duration of action and is less likely to cause tetanic contractions than ordinary pituitary extracts.

increasingly less responsive as the puerperium progresses, though its reactivity can be prolonged or restored if adequate doses of estrogens are given.

Pitressin is much more effective than pitocin in eliciting contractions in isolated strips of the pregnant and the nonpregnant human uterus. Pitocin, however, contracts the isolated virgin guinea-pig uterus while any action of pitressin in this respect is due to the presence of the contaminating oxytocic fraction, neither fraction being as yet completely separated from the other. The specific action of the oxytocic hormone on the isolated virgin guinea-pig uterus forms the basis of the official method for the bioassay of posterior-pituitary extracts.

In the normal parturient patient, posterior pituitary or its pressor fraction in therapeutic doses does not produce any appreciable effect on the blood pressure. In the patient with eclampsia or pre-eclampsia, however, there is a marked rise in blood pressure and a decrease in urine volume, conditions which might predispose to an eclamptic attack. Because of this and because the pressor fraction appears more prone to cause posterior-pituitary "shock," the use of the oxytocic fraction is to be preferred in obstetrics to the use of pitressin, or to pituitary extract containing approximately equal amounts of both the pressor and oxytocic fractions. Posterior-pituitary preparations are usually given intramuscularly. In emergencies when a prompt effect is desired they can be given intravenously, but a single dose should not exceed 0.2 units.

A clinical disadvantage of posterior pituitary is the evanescence of its oxytocic action, which usually does not last for more than 10 minutes. Various attempts have been made to delay the absorption of posterior pituitary and thus prolong its effect. Hofbauer introduced the application of the drug to the nasal mucosa but the absorption is difficult to control and overdoses may ensue. Pitocin tannate in oil, pituitary and thymus-gland combinations (*thymophysin* and

## PREPARATIONS

Prepared ergot B.P. Powdered and defatted ergot. 0.3-1 Gm.

*Liquid extract of ergot B.P. When freshly prepared, this contains not less than 0.06% of total ergot alkaloids, calculated as ergotoxine. 0.6-1.2 cc.*  
 Ergotamine tartrate U.S.P. 0.5 mg. by injection; 1 mg. orally

Ergotamine-tartrate tablets U.S.P. Usually 0.5 and 1 mg. tablets.  
 Ergotoxine ethanesulfonate B.P. 0.5-1 mg.

Ergonovine maleate U.S.P. Ergometrine B.P. 0.1-0.5 mg. Ergonovine-maleate tablets U.S.P. Usually 0.2 and 0.5 mg. tablets.

Ergonovine maleate injection U.S.P. Usually 0.2 mg. or 0.5 mg. in 1 cc.

Posterior-pituitary injection U.S.P.; B.P. Contains 1 unit per 0.1 cc. 0.2-1 cc.

Ampuls pitocin N.N.R. 1 cc. contains 10 oxytocic units. 0.3-1.0 cc.

Ampuls pitressin N.N.R. 1 cc. contains 20 pressor units. 0.3-1.0 cc.

Pitressin tannate in oil N.N.R. 1 cc. contains 5 pressor units. 0.3-1.0 cc.

Quinine hydrochloride U.S.P.; B.P. Quinine sulfate U.S.P.; B.P. 0.12-0.6 Gm.

## BIBLIOGRAPHY

## GENERAL

Davis, M. E.: Post-partum hemorrhage, *Am. J. Surg.* 48:154, 1940.  
 Davis, M. E., F. L. Adair and S. Pearl: The present status of oxytocics in obstetrics, *J.A.M.A.* 107:261, 1936.  
 Eastman, N. J.: The induction of labor, *Am. J. Obst. & Gynec.* 35:721, 1938.



successful in the stimulation of the uterus in primary inertia.

There has been considerable difference of opinion with regard to the action of epinephrine on the uterus. Certainly variations in response occur, depending on the species of the animal studied, the presence or absence of pregnancy and the experimental technics employed. Because the earlier work suggested that epinephrine abolished the spontaneous contractions of the uterus, the drug has been used clinically for the treatment of contraction rings during pregnancy. More recent work, however, indicates that epinephrine is probably of little or no value in such conditions, any apparent muscular relaxation being followed by increased motor activity. Furthermore, undesirable side effects from epinephrine may contribute to the patient's already weakened condition. Recently, there have been reports in the German literature of a new oxytocic "varon," obtained by methylating the two phenolic-OH groups of epinephrine. This drug is claimed to have an oxytocic effect but little or no pressor action.

### ABORTIFACIENTS

A wide variety of drugs have been used to bring on abortions. Usually employed by the laity, these drugs are, generally speaking, neither safe nor efficacious. The simplest of such drugs allegedly act by pelvic congestion and include the drastic purgatives and uterine stimulants. Particularly dangerous are the proprietary abortifacient pastes such as "utra-jel," "interruptin," "provocol" and "anti-gravid," which act by killing the fetus. They consist principally of soft soap and are deposited in the uterus by means of a special applicator. They may produce local effects such as inflammation, necrosis or prolonged bleeding as well as systemic effects including embolism, hemolysis or generalized septicemia.

- Hart, B. F., and V. Noble: Calcium and quinine in labor and post partum hemorrhage, *Am. J. Obst. & Gynec.* 45:692, 1943.
- Murphy, D. P.: The effect of estrogenic substance upon uterine motility during labor—a study of 42 patients with the Lorand Tocograph, *Surg., Gynec. & Obst.* 77: 433, 1943.
- Woodbury, R. A., and B. E. Abreu: Influence of epinephrine upon the human gravid uterus, *Am. J. Obst. & Gynec.* 48:706, 1944.

#### ABORTIFACIENTS

- Lewin, L.: Die Fruchtabtreibung durch Gifte und andere Mittel (ein Handbuch für Ärzte, Juristen, Politiker, Nationalökonomien), Berlin, Stilke (publisher), 1925.
- Straus, R., and N. de Nosaque: Effects of an abortifacient paste ("utra-jel") report of a death from its use and of an experimental study of its effects on rabbits and rats, *Arch. Path.* 39:91, 1945.
- Weilerstein, R. W.: Intrauterine pastes, *J.A.M.A.* 125: 205, 1944.

- Moir, C.: Oxytocic drugs and their use, *J. Obst. & Gynaec.* 51:247, 1944.
- Reynolds, S. R. M.: *Physiology of the Uterus*, New York, Hoeber, 1939.

## ERGOT

- Barger, G.: *Ergot and Ergotism*, London, Gurney and Jackson, 1931.
- Hartman, M. M.: Parenteral use of dihydroergotamine in migraine, *Ann. Allergy* 3:440, 1945.
- Lennox, W. G.: The use of ergotamine tartrate in migraine, *New England J. Med.* 210:1061, 1934.
- Moir, C.: The action of ergot preparations on the puerperal uterus—a clinical investigation with special reference to an active constituent of ergot as yet unidentified, *Brit. M. J.* 1: 1119, 1932.
- Moir, C., and C. S. Russell: An investigation of the effect of ergot alkaloids in promoting involution of the postpartum uterus, *J. Obst. & Gynaec.* 50:94, 1943.
- Nelson, E. E., and H. O. Calvery: Present status of the ergot question, *Physiol. Rev.* 18:297, 1939.
- Velkoff, A. S., and A. D. Ferguson: Bilateral dry gangrene of both lower extremities due to ergot, *Am. J. Obst. & Gynec.* 44:331, 1942.
- White, A. C.: A comparison of some of the ergot alkaloids; III. General pharmacology, *Quart. J. Pharm. & Pharmacol.* 17:95, 1944.

## POSTERIOR PITUITARY

- De Lee, J. B.: The use of solution of posterior pituitary in modern obstetrics, *J.A.M.A.* 115:1320, 1940.
- Moir C.: The effect of posterior lobe pituitary gland fractions on the intact human uterus. *J. Obst. & Gynaec.* 51:181, 1944.
- Sullivan, C. L., and R. J. Heffernan: Convulsions following the intravenous administration of pituitary extract, *Am. J. Obst. & Gynec.* 44:675, 1942.

## MISCELLANEOUS

- Brown, W. E., and V. M. Wilder: The response of the human uterus to epinephrine, *Am. J. Obst. & Gynec.* 45:659, 1943.

tion is not possible. In such cases, biologic assay is necessary. International or United States Pharmacopoeial standard preparations are available for most of the hormones, the strength of the endocrine preparations being usually expressed in terms of units of activity.

Endocrine preparations, with the exception of the thyroid and some of the steroid hormones, are ineffective by mouth because of their rapid destruction by the digestive juices or by the liver. The action of most hormones is slow in onset and is sustained over some period of time. Notable exceptions are epinephrine and posterior-pituitary extracts, which elicit prompt, short-acting effects.

In recent years, drugs having an antagonistic action towards endocrine glands have attracted considerable experimental and clinical attention. Alloxan has a selective toxic action on the beta cells of the islet tissue of the pancreas leading to a permanent diabetes mellitus. Thyroids related drugs interfere with the formation of the thyroid hormone and lead to a depression of basal metabolism in normal or hyperthyroid subjects. The relationship between the hormones themselves is a matter of considerable practical and theoretical importance. Thus, small doses of crude anterior lobe extracts stimulate the production of insulin (pancreatropic effect) while large doses cause degenerative changes in the islet cells leading to diabetes (diabetogenic effect). In addition, certain drugs may stimulate the formation or release of endocrins. Recent evidence suggests that yohimbine stimulates the anterior lobe of the pituitary gland, while the antidiuretic effect of a number of drugs has been thought to be mediated indirectly through an increased output of the antidiuretic hormone of the neural lobe.

## ANTERIOR-PITUITARY HORMONES

Anterior-lobe preparations have few therapeutic applications or uses at the present time despite the important

# Endocrins

ANTERIOR-PITUITARY HORMONES  
GONADOTROPINS  
SEX HORMONES  
ANDROGENS

ESTROGENS  
PROGESTINS  
ADRENAL CORTEX  
PREPARATIONS

Endocrins (hormones) are autopharmacologic substances normally elaborated by the endocrine or ductless glands. Use of glandular preparations is largely restricted to substitution or replacement therapy occasioned by surgical interference, congenital deficiency or disease. In some cases, only crude extracts are available. In others, the active principles have been isolated as chemical entities, while epinephrine, thyroxin, the sex hormones and a number of the adrenal-cortical steroids can be prepared synthetically. In addition, a number of synthetic preparations are available which are not identical with the natural hormones but which resemble them in some or all of their pharmacologic activities. Such compounds include the sympathomimetic amines (chap. 11); a variety of compounds having an activity simulating that of the sex hormones; and probably also desoxycorticosterone, which produces several of the physiologic effects of adrenal-cortex extracts.

Endocrins of known chemical constitution, such as thyroxin, epinephrine and the sex hormones, can be assayed by chemical methods. In general, however, hormones are not assayed by such procedures either because their composition is not established or because they are present in such minute quantities that physical or chemical identifica-

in 0.1 mg. of the prolactin standard. The usual assay procedure for prolactin is based on stimulation of the crop gland in pigeons.

## GONADOTROPINS

Gonadotropins are substances which stimulate the gonads and indirectly affect the secondary sex organs by increasing the output of the sex hormones. Sources of gonadotropins include the pituitary gland, human pregnancy urine, menopausal urine, and the serum of pregnant mares. Gonadotropic substances are also found in the urine of patients with chorionepithelioma and hydatidiform mole. None of the gonadotropins have been identified chemically though they are believed to be protein in nature.

The pituitary is thought to elaborate at least two gonadotropic substances: the *follicle-stimulating hormone* (FSH), whose gametogenic activity stimulates the development of the ovarian follicles and the seminiferous tubules, and the *luteinizing hormone* (LH), whose interstitial-cell stimulating effect leads to the formation of the corpus luteum and the secretion of the male sex hormone. At present, therapy with pituitary gonadotropins is still in the experimental stage because of the difficulties of obtaining sufficient quantities of the purified preparations and the uncertainties concerning the true nature of the defects in patients treated with such preparations.

The gonadotropic substance in human pregnancy urine is believed to be elaborated by the chorion and is known as *chorionic gonadotropin*. It is demonstrable in the urine soon after implantation of the egg. It differs from pituitary gonadotropin in that it has little or no follicle-stimulating effect on the ovaries of primates and in fact may even cause degenerative changes. It does, however, stimulate the testis and its chief clinical use is in cases of cryptorchidism in which nondescent of the testis is not due to a mechanical obstruction. While there have been reports on the successful

physiologic role of this gland. Clinical use is limited by the lack of suitably potent preparations and by the hazards of undesirable side effects. These undesirable effects may result not only through the action of contaminating principles in impure preparations, but also from the peculiar reciprocal relationships between the pituitary and the other glands, and by the development of allergic phenomena and antibody formation due to the protein nature of the anterior-pituitary principles.

A number of active principles have been isolated in a high degree of purity from the anterior pituitary. These include the growth, thyrotropic, adrenocorticotropic and gonadotropic substances. *Growth hormone preparations* have had some use in the treatment of dwarfism, but since they have usually been used in conjunction with other drugs, such as thyroid extract, it is difficult to assess their real value. The *thyrotropic principle* will relieve the symptoms of hypothyroidism of pituitary origin; however, it is of diagnostic interest only since such conditions respond readily to thyroid medication. The lactogenic hormone, *prolactin*, has been isolated in crystalline form. It stimulates the secretion of milk after the mammary glands have been suitably prepared by the sex hormones and has been used clinically for this purpose. Though its efficacy is questionable, its use has been reportedly attended with little or no undesirable effects. No anterior-lobe preparations have been accepted for inclusion in the U.S.P. or N.N.R. The N.F. contains whole pituitary, which must be given by mouth and is therefore almost certainly without effect.

**Standardization of Anterior-Pituitary Preparations:** International Standard preparations have been established for the thyrotropic and lactogenic hormones. One unit of thyrotropic activity is present in 0.25 mg. of the standard. Several assay methods are used which are based on the stimulation of the thyroid of the immature or hypophysectomized animal. One unit of lactogenic activity is present

Standardization of Gonadotropins. International Standard preparations are available for the assay of both chorionic and equine gonadotropins; 0.1 mg. of the International Standard of chorionic gonadotropin and 0.25 mg. of the International Standard of equine gonadotropin contain one unit of chorionic and equine gonadotropin respectively. Assay procedures may be based either on direct morphologic changes in the gonads or on secondary changes in the accessory sex organs provided it can be shown that these changes are not directly caused by contaminating substances. This can be done by means of control experiments with castrated animals.

## SEX HORMONES

The sex hormones can be classified into three groups, *androgens*, *estrogens* and *progestins*, which are remarkably similar in chemical structure but divergent in biologic activity. While androgens are, for the most part, elaborated in the testis and estrogens and progestins in the ovary, the various types are by no means peculiar to one sex only. Furthermore, these substances are produced not only by the gonads but also by the adrenal, placenta and, possibly elsewhere in the body.

The naturally occurring sex hormones are relatively inactive by mouth. A number of synthetic substances possessing androgenic, estrogenic or progestational activity have been developed which are active by mouth. Such preparations are less rapidly destroyed by the liver than the naturally occurring sex hormones.

## ANDROGENS

Androgens are substances possessing masculinizing activity which leads to the development and maintenance of secondary sex characteristics in the male. The naturally occurring androgens include testosterone, first isolated from bull testicles in 1934 and now prepared synthetically, and



use of chorionic gonadotropin in ovarian hypofunction and menstrual disorders, there is little evidence to support the use of the preparation in gynecologic practice. The combined use of pituitary and chorionic gonadotropins is said to induce a synergistic stimulatory action on the ovaries but reports on the clinical efficacy of such a combination are conflicting.

In species below primates, chorionic gonadotropin has a stimulatory action on the ovaries. This action forms the basis of the Aschheim-Zondek and the Friedman tests for pregnancy. In the Aschheim-Zondek test, urine is injected into mice on three successive days. The animals are then killed and the ovaries examined. The presence of blood-filled follicles or corpora lutea indicates that the subject from whom the urine was obtained is pregnant. The Friedman test uses rabbits. The urine extract is injected into the ear vein and 24 hours later the ovaries are examined by\* laparotomy. The presence of ovulated or hemorrhagic follicles is indicative of pregnancy. Positive responses will be given in these tests in other conditions in which chorionic gonadotropin is excreted, such as chorionepithelioma.

Equine gonadotropin obtained from the serum of pregnant mares has both follicle-stimulating and luteinizing activity, though whether these two effects are vested in the same or in separate principles is still undecided. Equine gonadotropin has been prepared in a high degree of purity. It has a prolonged action since it is metabolized very slowly in the human body and is not excreted by the kidney. While experimental findings would indicate its usefulness as a therapeutic agent in hypo-ovarianism, clinical trials have, for the most part, been disappointing. Hamblen and his co-workers believe that more promising results are obtained with a cyclic form of treatment in which equine gonadotropin is given during the first half of the menstrual cycle to cause follicle growth and ovulation and chorionic gonadotropin is given during the second half to promote luteinization.

the less active androstosterone and dehydroandrostosterone. These latter are found in the urine and may be of adrenal-cortical origin.

Androgens are used mainly for replacement therapy in castration and eunuchoidism. A prolonged effect may be obtained by parenteral administration of testosterone propionate in oil. Methyltestosterone is effective by mouth but large doses are required. Testosterone itself can also be used in the form of subcutaneously implanted pellets or as an ointment. Continued dosage of androgenic preparations leads to a restoration of secondary sex characteristics, such as growth and distribution of hair, pitch of voice and growth of external genitalia, and to a general improvement in the well-being of the patient. Androgen therapy does not restore impaired testicular function; on the contrary, further depression may occur due to a suppressive action on the gonadotropic hormones of the anterior pituitary. Its use is, therefore, questionable in cases of delayed maturity in which normal physiologic function might be ultimately established; in such cases, stimulation with gonadotropic preparations should be first tried.

Androgen therapy has been recommended for a variety of disorders in women, such as dysmenorrhea, functional uterine bleeding and menopausal symptoms. Its value in these conditions is questionable in view of its masculinizing action, which may lead to hirsutism and alterations in the pitch of the voice.

Standardization of Androgens. The international unit of androgenic activity is the activity contained in 0.1 mg. of the International Standard preparation of androstosterone. Androgen preparations are assayed biologically by comparing their growth-promoting action on the capon's comb with that of the standard.

## ESTROGENS

Estrogens are substances which, in addition to their

Naturally  
occurring  
androgens



Testosterone



Androsterone

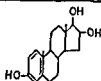


Dehydroandrosterone

Naturally  
occurring  
estrogens



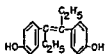
Estrone



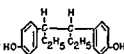
Estriol



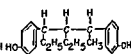
Estradiol



Diethylstilbestrol

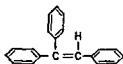


Hexestrol

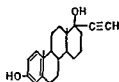


Benzestrol ;

Synthetic  
estrogens

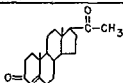


Triphenylethylene

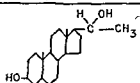


Ethinylestradiol

Naturally  
occurring  
progesterones



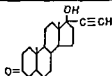
Progesterone



Pregnanediol

(Inactive urinary excretion  
product of progesterone)

Synthetic  
progesterones



Pregnenolone  
(Ethinyltestosterone)

The introduction of synthetic estrogens was the outcome of a series of investigations undertaken in 1933 by Dodds and his co-workers, who were the first to demonstrate that estrogenic activity was not confined to substances with a sterol nucleus. Of the several hundred substances shown to possess estrogenic activity, only a few have found clinical use. These include diethylstilbestrol, hexoestrol, benzestrol (octofollin) and triphenylethylene. Another compound which should perhaps be classified as a synthetic estrogen is ethinylestradiol, a modified natural sex hormone. It is probably the most active estrogen known; it is effective by mouth, although its metabolism by the liver is apparently as rapid as that of free estradiol. The activity of triphenylethylene and related compounds is actually enhanced by passage through the liver suggesting their breakdown into more potent compounds.

**Biologic Effects.** Biologic effects of estrogen include hyperplasia of the vaginal epithelium with cornification of the superficial layers; proliferation of the myometrium and endometrium; increase in weight and blood supply of the uterus; growth of the mammary gland and suppression of the secretion of pituitary gonadotropin.

**Therapeutic Uses.** Clinically, estrogens are used as replacement therapy in primary disorders of, defects in or insufficiency of ovarian function, for the relief of vasomotor and nervous disturbances of natural or surgical menopause, and for the relief of senile or menopausal vaginitis. Before the introduction of sulfonamides, the estrogens found wide use in the treatment of gonorrheal vaginitis in children since they produce a cornified epithelium and an acid reaction in the vagina unsuitable for the growth of bacteria. Estrogens have been used for the suppression of lactation, their action possibly being due to a reduction of the secretion of the lactogenic hormone by the anterior pituitary. In 1941, Huggins showed that carcinoma of the prostate could be at least temporarily arrested by castration.

distributed in nature and have been obtained from both plant and animal sources. The most important of the naturally occurring estrogens are the follicular hormones which develop and maintain the secondary sex characteristics in the female. The main physiologic source of these hormones is the ovary; during pregnancy, however, the placenta probably assumes the chief burden of secretion. Commercially, the main source of natural estrogens is the urine of pregnant mares.

Estrogens are normally inactivated by the liver, probably by conjugation. Liver damage or inanition retards this inactivation, and may lead to manifestations of excessive estrogen activity. The tolerance for estrogens is greatly increased during pregnancy, at which time as much as 1,000 times the ordinary dose has been given without untoward effects.

**Natural Estrogens.** Three natural estrogens are available in crystalline form for therapeutic use: *estradiol*, obtained from ovaries and pregnancy urine; *estriol*, obtained from placental tissue and pregnancy urine; and *estrone*, obtained from the urine of pregnant mares. Preparations of highly purified noncrystalline estrogens from pregnant human or pregnant mare urine are also available. The activity of these preparations, known as *solutions of estrogens*, is almost entirely due to estrone.

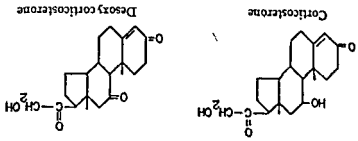
**Synthetic Estrogens.** In addition to the natural estrogens, a number of synthetic products with qualitatively similar biologic effects have been introduced for clinical use. These preparations have the advantages of cheapness and of being active by mouth, probably because they are less rapidly metabolized by the liver than the natural estrogens. For the same reason, they are more toxic than the natural estrogens. Their toxicity is not of great clinical importance since untoward reactions, chiefly gastro-intestinal upsets, are minimal in therapeutic doses.

are other sources of this hormone. It is quite similar chemically and to a certain extent biologically to the hormones of the testis and adrenal cortex. It is apparently metabolized to pregnandiol, a physiologically inert product which is excreted in the urine and which is believed to be an index of corpus luteum activity. Commercial preparations are for the most part prepared synthetically from stigmasterol. Progesterone is inactive by mouth and is usually administered intramuscularly in oil. A synthetic progestin, pregnenolone (ethinyloestosterone) is active by mouth, but doses from five to ten times the parenteral dose of progesterone are required.

Data concerning the clinical value of progesterone therapy are still inconclusive. Its use appears to be warranted in cases of habitual or threatened abortion in early pregnancy when corpus luteum insufficiency is suspected. It has also been used in cases of dysmenorrhea because of its alleged quieting action on the uterine musculature and in cases of functional bleeding resulting from overactivity of estrogens in the absence of corpus luteum activity.

Standardization of Progestins. The International Standard preparation of progesterone contains one unit of activity in 1.0 mg. The assay procedure is based on progestational changes in the uterus of the immature or ovariectomized rabbit.

### ADRENAL CORTEX



At least thirty steroids have been isolated from the adrenal cortex, many of which have no apparent biologic activity.

cases in which surgical castration is impractical, physiologic castration with estrogens by virtue of an inhibitory effect on the pituitary gonadotropins has been reported to give promising results. Estrogen therapy also relieves post-castration symptoms in the male, which frequently resemble those of the menopause.

**Estrogens as Carcinogenic Substances.** Large doses of estrogens have been shown to increase the incidence of cancer in susceptible strains of animals, while cancer of the prostate is apparently greatly stimulated by the male sex hormone. While the causal relationship between cancer and the sex hormones in humans has not been established, many investigators feel that prolonged use of these substances is contraindicated in persons suffering from cancer or who have a familial history of cancer. For this reason alone, the indiscriminate use of proprietary cosmetics containing estrogens may lead to serious consequences and is certainly unwarranted.

**Standardization of Estrogens.** International Standard preparations of estrone and estradiol monobenzoate are available, each containing one unit of activity in 0.1 micrograms. It is not feasible to assay against a standard any estrogen other than that of which the standard is composed because of differences in rates of penetration and of metabolism of the various estrogens. The chief assay methods are the examination of vaginal smears in rats and mice and the weight increase of the uterus of castrated rats.

### PROGESTINS

Progestins are substances producing progestational changes in the uterus which are suitable for implantation of the ovum and for maintenance and development of the embryo. *Progesterone* is a naturally occurring progestin. It is elaborated by the corpus luteum during the second half of the menstrual cycle and also, during gestation, by the placenta. The adrenals and probably also the testis

jection. Desoxycorticosterone is not active by mouth. It can be implanted in the form of pellets to give a prolonged effect. A 125 mg. pellet of desoxycorticosterone acetate may satisfactorily control the symptoms of adrenal insufficiency for a year or more; patients require supplementary injections of adrenal-cortical extracts in cases of emergencies such as those induced by intercurrent infections. Further improvements in the treatment of adrenal insufficiency can be expected with the introduction of synthetic corticosterone-like compounds, capable of improving the carbohydrate metabolism and muscular efficiency.

**Assay of Adrenal-Cortical Preparations.** Adrenal-cortical preparations are assayed on adrenalectomized animals. No official standard is available as yet. Potency is frequently expressed in terms of the dog unit, which is defined as the minimum daily dose per kilogram of body weight necessary to maintain a dog for a period of from 7 to 10 days without loss of body weight and elevation of nonprotein nitrogen level in the blood.

## PREPARATIONS

Chorionic gonadotropins N.N.R. 200-500 units.  
 Testosterone propionate U.S.P. 25 mg. intramuscular.  
 Methyltestosterone U.S.P. 5-10 mg. oral or sublingual.  
 Methyltestosterone tablets U.S.P. Usually 5 and 10 mg. tablets.  
 Estrone U.S.P. Oestrone B.P. 1 mg.  
 Estrogenic substances (water soluble) N.N.R. Largely sodium estrone sulfate 1-3 mg.  
 Estrogenic substances (water insoluble) N.N.R. Largely estrone 1,000-10,000 units.  
 Estradiol U.S.P. 0.2 mg.  
 Estradiol benzoate U.S.P. Oestradiol monobenzoate B.P. 1 mg.  
 Diethylstilbestrol U.S.P. Stilboestrol B.P. 0.5 mg.



Among the physiologically active compounds are the corticosterone and the desoxycorticosterone groups of compounds and the sex hormones. In addition, the amorphous fraction remaining after the known steroid hormones have been extracted will prolong the life of adrenalectomized animals, indicating the presence of further unidentified principles.

The main use of adrenal-cortical extracts is in the treatment of Addison's disease and other adrenal insufficiencies. In such conditions, sodium chloride and water are rapidly lost by the body, while potassium is retained. These changes in electrolyte balance lead to dehydration, reduction of blood-plasma volume and hemoconcentration. In addition, there are serious disturbances in carbohydrate metabolism. Absorption of glucose from the gastro-intestinal tract is impaired, glucose metabolism is increased and glycogen stores become depleted. Symptoms include weakness and fatigability, loss of weight and increased pigmentation of the skin.

Mild cases of adrenal insufficiency can be controlled by the administration of sodium chloride. More severe cases require supplemental treatment with adrenal-cortical extracts or with the synthetic preparation, desoxycorticosterone, which is available as the acetate. Adrenal-cortical extracts are usually prepared from fresh beef adrenals and vary greatly in their activity. Desoxycorticosterone has the advantage of being less expensive and more easily standardized. It has, however, little or no effect on the carbohydrate metabolism, which is apparently controlled by the corticosterone group of hormones. Furthermore, it may lead to a dangerous retention of water, which may result in hypertension, cardiac damage or edema of the lungs and other tissues.

Adrenal-cortical extracts are active by mouth, but their effects by this route are unpredictable and large amounts are required so that they are usually administered by intramuscular, subcutaneous or occasionally by intravenous in-

Young, F. G.: Functions of the pituitary gland (anterior lobe), *Practitioner* 154: 129, 1945.

#### GONADOTROPINS

Davis, M. E., and A. A. Hellbaum: Present status of gonadotropic therapy in gynecologic practice, *J. Clin. Endocrinol.* 3: 517, 1943.

Goldzieher, M. A.: Treatment of menstrual disorders with prolactin, *J. Clin. Endocrinol.* 5: 132, 1945.

Gusman, H., and M. A. Goldzieher: Synergism between pituitary extracts and chorionic gonadotropins, *Endocrinology* 29: 931, 1941.

Hamblen, E. C., and C. D. Davis: Treatment of hypoovarianism by the sequential and cyclic administration of equine and chorionic gonadotropins—so-called one-two cyclic gonadotropic therapy—summary of 5 years' results, *Am. J. Obst. & Gynec.* 50: 137, 1945.

Zondek, B., and F. Sulman: The mechanism of action and metabolism of gonadotropic hormones in the organism, *Vitamins & Hormones* 3: 297, 1945.

#### SEX HORMONES

Burrows, H.: Biological Actions of Sex Hormones, Chicago, Cambridge Univ. Press, 1945.

Dodds, E. C.: Hormones in cancer, *Vitamins & Hormones* 2: 353, 1944.

Dodds, E. C.: Possibilities in the realm of synthetic estrogens, *Vitamins & Hormones* 3: 229, 1945.

Fergusson, J. D., and W. Pagel: Some observations on carcinoma of the prostate treated with oestrogens as demonstrated by serial biopsies, *Brit. J. Surg.* 33: 122, 1945.

Fluhmann, C. F.: Clinical use of extracts from the ovaries and of synthetic products having similar actions, *J. A. M. A.* 125: 1, 1944.

Freed, S. C.: The treatment of pre-menstrual distress, with special consideration of the androgens, *J. A. M. A.* 127: 377, 1945.

Greenhill, J. P.: The use and potency of synthetic estrogens, *Am. J. Obst. & Gynec.* 44: 475, 1942.

Hamblen, E. C.: Endocrine therapy in gynecology and obstetrics, *Am. J. Obst. & Gynec.* 45: 147, 1943.

Diethylstilbestrol tablets U.S.P.; B.P. Usually 0.1, 0.5 and 1.0 mg. tablets.

Diethylstilbestrol capsules U.S.P. Usually available containing following amounts of diethylstilbestrol, 0.1, 0.5 and 1.0 mg.

Benzestrol N.N.R. 2-5 mg.

Hexestrol N.N.R. 2-3 mg.

Ethinyl Estradiol N.N.R. 0.5 mg.

Mestilbol N.N.R. 0.5-1.0 mg.

Progesterone U.S.P. 5 mg. intramuscular.

Desoxycorticosterone acetate U.S.P. Dose determined by needs of patient.

Adrenal cortex extract N.N.R.

## BIBLIOGRAPHY

### GENERAL

Glandular Physiology and Therapy, A. M. A., Chicago, 1942.

Greene, R.: The materia medica of endocrinology, *Practitioner* 154: 157, 1944.

Sevringhaus, E. L.: Endocrine Therapy in General Practice, Chicago, Yr. Bk., Pub. 1945.

### ANTERIOR-PITUITARY HORMONES

Evans, H. M.: The hypophyseal growth hormone—its separation from the hormones stimulating the thyroid, gonads, adrenal cortex and mammary glands, *A. Res. Nerv. & Ment. Dis.* 17: 175, 1938.

Friedgood, H. B.: Endocrine function of the hypophysis, New York, Oxford, 1946.

Rynearson, E. H.: Hormones of the anterior lobe of the pituitary body—a clinical review, *J.A.M.A.* 125: 5, 1944.

Smith, P. E.: Relations of the activity of the pituitary and the thyroid glands, *Harvey Lect.* 25: 129, 1929-1930.

Van Dyke, H. B.: The Physiology and Pharmacology of the Pituitary Body, Chicago, Univ. Chicago Press, 1936.

Winson, S. G.: The lactogenic effect of prolactin in the human being, *Am. J. Obst. & Gynec.* 46: 545, 1943.

role in pigmentary changes in higher vertebrates. It has  
There is little evidence to indicate, however, that it plays a  
persion of pigment granules in the skin chromatophores.  
vertebrates (fish, amphibians and reptiles); it causes a dis-  
physiologic or pharmacologic activity in man. In lower  
intermedin. The intermediate-lobe hormone has no known  
hed hormones are actually vested in a single molecule.

the body the various activities associated with the two puri-  
arations, there is considerable evidence to indicate that in  
oxytocic hormones have been obtained as highly pure prep-  
are present in the neural lobe. Although the pressor and the  
the anterior lobe, while the pressor and oxytocic hormones  
(birds, cetaceans and the armadillo) intermedin is present in  
as intermedin. In animals which lack an intermediate lobe  
*diuretic hormone*. The intermediate-lobe hormone is known  
which is generally thought to be identical with the *anti-*  
*hormone* (pitocin) and the *pressor hormone* (pitressin),  
properties. The neural-lobe hormones consist of the *oxytocic*  
and since their active principles have quite similar chemical  
the two lobes cannot easily be separated in most species  
both the neural- and the intermediate-lobe hormones since  
Commercial posterior-pituitary preparations consist of

# POSTERIOR PITUITARY

## PREPARATIONS

INSULIN	PARATHYROID
THYROID	LIPOCALIC
	THYMUS

(Continued)

# Endocrins

- Heckel, N. J.: Evaluation of sex hormones in the treatment of benign prostatic hypertrophy, carcinoma of the prostate and other diseases of the genito-urinary system, *J. Clin. Endocrinol.* 41:166, 1944.
- Huggins, C.: Endocrine control of prostatic cancer, *Science* 97:541, 1943.
- Morgan, T. N.: The male sex hormones, *Practitioner* 154:149, 1944.
- Solmssen, U. V.: Synthetic estrogens and the relation between their structure and their activity, *Chem. Rev.* 37:481, 1945.
- Stoddard, F. J.: The abuse of endocrine therapy in gynecology, *J.A.M.A.* 129:508, 1945.
- Thompson, W. O.: Uses and abuses of the male sex hormone, *J.A.M.A.* 132:185, 1946.

#### ADRENAL CORTEX

- Goldzieher, M. A.: *The Adrenal Glands in Health and Disease*, Philadelphia, Davis, 1945.
- Grollman, A.: *The Adrenals*, Baltimore, Williams & Wilkins, 1936.
- Reichstein, T., and C. W. Shoppee: The hormones of the adrenal cortex, *Vitamins & Hormones* 1:345, 1945.
- Swingle, W. W., and J. W. Remington: The role of the adrenal cortex in physiological processes, *Physiol. Rev.* 24:89, 1944.
- Thorn, G. W.: Clinical use of extracts from adrenal cortex and of synthetic products having similar actions, *J.A.M.A.* 125:10, 1944.
- Williams, R. H., J. L. Whittenberger, G. W. Bissell and A. R. Weinglass: Treatment of adrenal insufficiency, *J. Clin. Endocrinol.* 5:163, 1945.

in the neural lobe of the pituitary gland or in the supra-optico-hypophyseal tracts. It is characterized by the excretion of large volumes of urine of low specific gravity accompanied by an abnormally great thirst, which is probably secondary to the polyuria. Such patients may excrete 10 to 20 liters of urine per day. Administration of posterior pituitary causes a return to normal of the urine secretion and of the water intake. The antidiuretic effect is believed to be due to an increased absorption of water by the kidney tubules and a decreased absorption of salt. It has been suggested that the role of the hormone in the body is to maintain an equable water balance, acting in an antagonistic fashion to the adrenal cortex and to a diuretic substance in the anterior lobe. Removal or destruction by disease of the entire pituitary does not lead to the development of diabetes insipidus, while removal or destruction of the anterior lobe alleviates diabetes insipidus.

The most satisfactory preparation for the treatment of diabetes insipidus is pitressin tannate in oil. It was introduced by Greene and January in 1941 in an attempt to obtain a more prolonged effect than that afforded by aqueous solutions of posterior pituitary. The effect of pitressin tannate in oil lasts from 45 to 60 hours following a single injection of 5 units, while a similar dose of ordinary posterior-pituitary extract is effective for only some 4 to 6 hours. Intranasal absorption of posterior pituitary is also quite satisfactory; pituitary powder may be applied as a snuff or pledgets of cotton soaked in posterior-pituitary solution may be inserted in the nostrils. Overdosage of posterior pituitary may lead to a dangerous retention of water.

The vasoconstrictor action of posterior pituitary has led to its use as a styptic. It is of particular value in operations such as prostatic resections and tonsillectomies, in which excessive bleeding may occur, obscuring the operative field and contributing to surgical shock. If the drug is too rapidly absorbed there may be gastro-intestinal cramps and evacua-

been suggested that pigmentary degeneration of the retina may involve the intermediate-lobe hormones, but McDonald and Adler in a series of well-controlled experiments were unable to find any support for this theory. It has been advocated in the treatment of vitiligo, but it is probable that any apparent improvement is due to a nonspecific irritant effect. An increased excretion of intermedin has been reported in pregnancy and various pathologic conditions, but these results are undoubtedly due to the nonspecific nature of the assay procedure used, since they cannot be confirmed when a hypophysectomized animal is used as the test object.

**Neural-Lobe Hormones.** Pharmacologic effects evoked by injection of posterior-lobe extracts include an increase in blood pressure in the anesthetized mammal; suppression of urine secretion; stimulation of the gut musculature; constriction of blood vessels; increase in blood sugar; stimulation of the uterine musculature; and a fall in blood pressure in the fowl. In 1928, Kamm succeeded in separating the posterior lobe into two extracts with different effects. One fraction, the oxytocic, causes uterine stimulation and a fall in blood pressure in the bird, while the other, the pressor, causes *antidiuretic and pressor effects, diminished cardiac output*, probably due to coronary constriction, and stimulation of the gut. Both fractions have been shown to raise the blood sugar and to antagonize the effect of insulin. As yet the fractions have not been prepared completely free from each other; commercial preparations of the separate fractions contain about 90 per cent of one and 10 per cent of the other. Both fractions contain appreciable amounts of the intermediate-lobe hormone.

**Clinical Use of Posterior-Lobe Extracts.** The use of posterior pituitary as an oxytocic drug is discussed in Chapter 19. Preparations of posterior pituitary or of the pressor fraction are used in the treatment of diabetes insipidus. This condition is believed to be caused by a decreased secretion of the antidiuretic (pressor) hormone due to lesions

dispersion of pigment granules in the normal animal by virtue of a stimulatory action on the pituitary.

## INSULIN

Insulin is a simple protein elaborated by the islet tissue of the pancreas which affects the intermediary metabolism of carbohydrates and lipids and relieves the symptoms of diabetes mellitus. It is prepared commercially from the pancreases of cattle and of hogs. It was one of the first hormones to be prepared in crystalline form. While its chemical structure has not been fully established, over 95 per cent of the nitrogen has been accounted for in the form of amino acids, with a high proportion containing sulfur. Zinc is an essential part of the molecule, and the addition of zinc or of certain other heavy metal salts greatly facilitates crystallization. Insulin is inactive by mouth because of its large molecular size and its sensitivity to digestion by pepsin, trypsin and acids. Parenteral administration results in a rapid lowering of the blood sugar, increased deposition of glucose in the liver and muscles, increased respiratory quotient and decreased excretion of ketone bodies.

The relationship of the pancreas to diabetes mellitus was first established experimentally in 1889 by von Mering and Minkowski, who showed that depancreatized dogs developed symptoms essentially similar to those of diabetes mellitus in man. In 1922, Banting and Best, in Macleod's laboratory, succeeded in preparing a pancreatic extract which alleviated the diabetic symptoms of such animals, thus fully establishing the endocrine function of the gland. The active principle was called *insulin* by Banting and his associates, a name suggested by Sharpey-Schafer in 1916 when the existence of such a substance was hypothetical. The experimental work led to the preparation of insulin extracts suitable for clinical purposes by Collip and to the isolation of the hormone in crystalline form by Abel and his co-workers in 1927.



tion of the bowels. The use of posterior pituitary is contraindicated in heart disease because of its coronary-constricting action and in pregnancy because of its oxytocic effect. The addition of epinephrine or ephedrine may antagonize the effect of pituitary on the coronary vessels and has a further advantage of prolonging the pressor effect of posterior pituitary.

Posterior pituitary, because of its stimulating action on the bowel musculature, has been used for the treatment of postoperative paralytic ileus and to allay distention. Fairly large doses are required to produce this effect. It has been demonstrated experimentally that large doses of posterior pituitary may give rise to gastric ulcers because of local ischemia caused by vasoconstriction. There is some clinical evidence to indicate that gastric ulcers have followed the use of posterior pituitary.

**Hypersensitivity to Posterior-Pituitary Extracts.** Occasional cases of hypersensitivity to posterior-pituitary preparations have been reported. Symptoms include pallor, rapid pulse, fall in blood pressure, air hunger, sense of impending death and, in some cases, edema and unconsciousness. Rapid relief may be obtained with epinephrine injections.

**Standardization of Posterior Pituitary.** An International Standard preparation of posterior pituitary is available for assay purposes. It contains 1 unit of activity (pressor, antidiuretic, oxytocic and intermedin) in 0.5 mg. The official United States and British methods of assay cover only oxytocic activity and are based on the production of contractions in the excised uterus of the virgin guinea pig. Oxytocic activity can also be assayed by the fall of blood pressure in the fowl. The pressor (antidiuretic) hormone can be assayed by the rise of blood pressure in the anesthetized cat or dog or by the production of antidiuresis in the rat, mouse or dog. Assays for the intermediate-lobe hormones should be based on melanophore-dispersing activity in the hypophysectomized animal, since a number of substances will cause a

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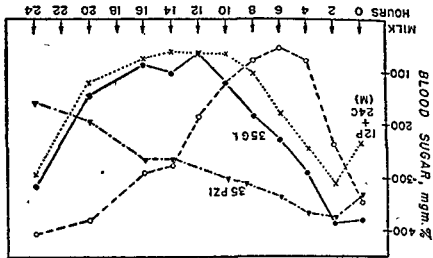
## INSULIN

Insulin is a simple protein elaborated by the islet tissue of the pancreas which affects the intermediary metabolism of carbohydrates and lipids and relieves the symptoms of diabetes mellitus. It is prepared commercially from the pancreases of cattle and of hogs. It was one of the first hormones to be prepared in crystalline form. While its chemical structure has not been fully established, over 95 per cent of the nitrogen has been accounted for in the form of amino acids, with a high proportion containing sulfur. Zinc is an essential part of the molecule, and the addition of zinc or of certain other heavy metal salts greatly facilitates crystallization. Insulin is inactive by mouth because of its large molecular size and its sensitivity to digestion by pepsin, trypsin and acids. Parenteral administration results in a rapid lowering of the blood sugar, increased deposition of glucose in the liver and muscles, increased respiratory quotient and decreased excretion of ketone bodies.

The relationship of the pancreas to diabetes mellitus was first established experimentally in 1889 by von Mering and Minkowski, who showed that depancreatized dogs developed symptoms essentially similar to those of diabetes mellitus in man. In 1922, Banting and Best, in Macleod's laboratory, succeeded in preparing a pancreatic extract which alleviated the diabetic symptoms of such animals, thus fully establishing the endocrine function of the gland. The active principle was called *insulin* by Banting and his associates, a name suggested by Sharpey-Schafer, in 1916 when the existence of such a substance was hypothetical. The experimental work led to the preparation of insulin extracts suitable for clinical purposes by Collip and to the isolation of the hormone in crystalline form by Abel and his co-workers in 1927.

**Clinical Uses of Insulin.** **DIABETES MELLITUS.** The chief use of insulin is in the treatment of diabetes mellitus, a disorder caused by inadequate endogenous insulin production. The major problem in the treatment lies in trying to duplicate by injection the function of the normal pancreas in supplying insulin according to the varying demands of the body. Amorphous or crystalline insulins are rapidly absorbed into the blood stream on subcutaneous injection, causing marked fluctuations in blood sugar and necessitating frequent dosage. Early efforts to delay absorption by the use of oily suspensions or by the concomitant injection of local vasoconstrictors were not very successful. In 1935, however, Hagedorn and his associates prepared a slowly absorbed preparation, *protamine insulinate*, by combining insulin with a protamine obtained from fish sperm. This was soon replaced by the even more effective *protamine zinc insulin* made by Scott and Fisher by adding zinc to insulin before the addition of protamine. This compound or complex is very satisfactory in cases of mild diabetes in which a single daily injection suffices to control the disease by a relatively constant action throughout the 24-hour period (see page 267). In more severe cases, doses sufficiently large to control the daytime blood glucose may lead to a hypoglycemia at night when the carbohydrate intake is reduced. In some cases, a satisfactory compromise can be reached by two morning injections, one of regular insulin and one of protamine zinc insulin. Since the injection of two preparations requiring different dosage tends to be confusing to the patient, efforts have been made to modify the protamine zinc insulin to contain a proportion of the insulin in readily absorbable form. Such preparations can be prepared by adding equal or greater amounts of regular insulin to the protamine zinc insulin or by modifying ordinary protamine zinc insulin so that its protamine zinc content is lowered. The exact chemical nature of the resulting products is not known but their effect is

mediate in promptness, intensity and duration of action between protamine zinc insulin and ordinary insulin. Other insulins with a retarded action include globin insulin, a combination of insulin and globin prepared from beef hemoglobin, and histone insulin, insulin combined with histone from the thymus. The duration of action of these preparations is intermediate between protamine zinc insulin and ordinary insulin. However, since their onset of action is as delayed as that of protamine zinc insulin, they will not control the postprandial hyperglycemia of severe cases of diabetes mellitus. Globin insulin is a clear acid solution



Twenty-four hour blood-sugar curves on the same patient with different forms of insulin. All food was withheld other than milk, which was given every 2 hours. (PZI = protamine zinc insulin; G.I. = globin insulin; C.I. = crystalline insulin; P + C = mixture of protamine zinc insulin and crystalline insulin. The dosage of each preparation is expressed in units.)

From H. T. Ricketts: Certain Aspects of the newer insulins, Illinois Med. J. 87:133, 1945.

which is precipitated by tissue fluids. Since its duration of effect depends upon the degree to which it is precipitated, its action is less predictable than that of protamine zinc insulin. Furthermore, some patients complain of a burning

**Clinical Uses of Insulin.** **DIABETES MELLITUS.** The chief use of insulin is in the treatment of diabetes mellitus, a disorder caused by inadequate endogenous insulin production. The major problem in the treatment lies in trying to duplicate by injection the function of the normal pancreas in supplying insulin according to the varying demands of the body. Amorphous or crystalline insulins are rapidly absorbed into the blood stream on subcutaneous injection, causing marked fluctuations in blood sugar and necessitating frequent dosage. Early efforts to delay absorption by the use of oily suspensions or by the concomitant injection of local vasoconstrictors were not very successful. In 1935, however, Hagedorn and his associates prepared a slowly absorbed preparation, *protamine insulinate*, by combining insulin with a protamine obtained from fish sperm. This was soon replaced by the even more effective *protamine zinc insulin* made by Scott and Fisher by adding zinc to insulin before the addition of protamine. This compound or complex is very satisfactory in cases of mild diabetes in which a single daily injection suffices to control the disease by a relatively constant action throughout the 24-hour period (see page 267). In more severe cases, doses sufficiently large to control the daytime blood glucose may lead to a hypoglycemia at night when the carbohydrate intake is reduced. In some cases, a satisfactory compromise can be reached by two morning injections, one of regular insulin and one of *protamine zinc insulin*. Since the injection of two preparations requiring different dosage tends to be confusing to the patient, efforts have been made to modify the *protamine zinc insulin* to contain a proportion of the insulin in readily absorbable form. Such preparations can be prepared by adding equal or greater amounts of regular insulin to the *protamine zinc insulin* or by modifying ordinary *protamine zinc insulin* so that its protamine and zinc content is lowered. The exact chemical nature of the resulting products is not known but their action is inter-

has been largely replaced by simpler techniques employing metrazol or electric convulsions.

**Malnutrition.** Insulin is used to stimulate the appetite in malnutrition and during convalescence. Small doses are given three times daily before meals, until a satisfactory gain in weight is achieved. It has been postulated that the improvement in appetite following insulin results from increased hunger sensations due to hypoglycemia and hypermotility of the stomach or from improved digestion due to increased gastric and biliary secretion. It is possible, however, that the improved appetite is a psychologic effect.

**Insulin Resistance and Insulin Sensitivity.** Occasionally, patients manifest a resistance to insulin which may be idiopathic in nature or associated with infection, fever, liver disease or overactivity of the thyroid, adrenal or pituitary glands. In severe cases, patients may fail to respond to doses greater than 1,000 units. In addition to insulin resistance, some individuals are remarkably resistant to the effects of hypoglycemia per se. In such cases, unconsciousness cannot be induced in insulin-shock therapy despite a greatly lowered blood glucose.

Insulin hypersensitivity may be manifested by a local reaction or a severe generalized reaction resembling anaphylactic shock. Hypersensitivity may be due to the insulin itself, to extraneous pancreatic substances, or to added substances, such as protamine. Desensitization can be effected by very small doses at frequent intervals. Because of the possibility of insulin sensitivity, all diabetic patients should be first treated with small doses of the drug. Granulomas or fatty hypertrophy may develop at the site of insulin injection. The former are nonspecific inflammatory reactions while the latter is specific to insulin, the condition being known as insulin lipohypertrophy. The opposite condition, namely, atrophy of the subcutaneous fat, also occurs. These disfiguring complications are not



sensation on injection, though local reactions are said to be less frequent than with protamine zinc insulin.

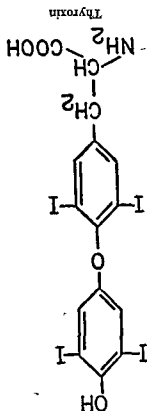
While insulin alleviates the symptoms of diabetes rather than curing the underlying disorder, there is considerable evidence to indicate that the islet cells of the pancreas have some regenerative powers. Brush has introduced a new regimen in the treatment of diabetes of recent onset in children. When treatment is begun, insulin is administered to the limit of tolerance. After about 10 days of such dosage levels, shock develops, presumably because of the increased secretion of endogenous insulin as a result of functional recovery of the islet cells. The daily insulin requirement then progressively decreases until a stable level is reached, usually after some 20 or 30 days of treatment.

Insulin dosage should always be expressed in terms of units and should be based on the needs of the patient. Mild cases can usually be controlled by diet alone. In more severe cases, the initial dose should be fairly low (10 to 20 units, once or twice a day, depending on the preparation used) and gradually adjusted so that the patient's blood-sugar level is kept between 100 and 150 mg. per cent. Extremely severe cases may require 80 or more units. While most diabetics can be controlled by one of the modified forms of insulin, ordinary insulin should be available for emergency intravenous use, for the rapid relief of severe hyperglycemia or for the treatment of diabetic coma.

**Shock Treatment of Mental Disorders.** Insulin has been used for the shock treatment of schizophrenia and certain other mental disorders since 1932. Its value was accidentally discovered by Sakel, who noted a marked improvement in the mental condition of his patients following an attempt to treat withdrawal symptoms in morphine addicts with insulin. Treatment consists of daily injections of insulin, starting with from 10 to 20 units and gradually increasing the dosage until unconsciousness is produced. The treatment requires careful medical and nursing care and for this reason

severe states result in myxedema in adults or cretinism in children.

The iodine-containing amino acid *thyroxin* is the only compound with appreciable activity that has been isolated from the thyroid. Thyroxin was first isolated in 1915 by



Kendall but its chemical constitution was not determined until 1927 when Harington and Barger succeeded in preparing it synthetically. There is still doubt as to whether thyroxin is the form of the circulating hormone or whether it represents a degradation product. The presence of an unidentified active compound is suggested by the fact that the physiologic activity of the gland is related to its total organic iodine content rather than to its thyroxin-iodine content.

common but when present may result in poor absorption of insulin.

**Standardization of Insulin.** The International Standard preparation of insulin is a crystalline zinc-insulin preparation which contains 22 units of activity per milligram. The U.S.P. method of assay is based on the lowering of the blood sugar in rabbits. The official British method is based on the production of convulsions in mice.

**Hyperinsulinism.** Excessive insulin results in a proportional decrease in blood glucose, giving rise to a characteristic set of symptoms, referred to as hyperinsulinism. This condition may arise from an overdose of insulin or from hypersecretion from the islet tissue and is characterized by weakness, fatigue, disorientation and unconsciousness. Treatment consists of the intravenous administration of glucose if the patient is comatose or the administration of carbohydrates by mouth if the condition is less severe.

Recently it has been shown that diabetes can be induced experimentally by the intravenous injection of the drug *alloxan*, which has a selective toxic action on the islet cells of the pancreas. Attempts to treat islet-cell tumors with this drug have not as yet proved very successful, though some amelioration of symptoms has been reported. The effect of *alloxan* on the pancreas is in contrast to that of *thiourea* on the thyroid; both drugs suppress the overactivity of an endocrine organ, but whereas *thiourea* acts by interfering with the manufacture of the thyroid hormone, *alloxan* has a necrotizing effect on the cells which elaborate insulin. Except in small doses, the action of *alloxan* is therefore irreversible.

## THYROID

The thyroid gland exercises a general stimulatory effect on the oxidative processes of the body. Its activity is in turn regulated by the thyrotropic hormone of the anterior pituitary. Mild hypothyroidism is characterized by a lowered basal metabolic rate and increased fatigability. More

medical supervision and even then it is of questionable soundness. The danger of the uncontrolled use of thyroid preparations has led to their being available in many regions only on a doctor's prescription.

Standardization of Thyroid Preparations. Thyroid preparations are standardized by their content of iodine in thyroid combination. The United States Pharmacopoeia requires that thyroid contain not less than 0.17 per cent and not more than 0.23 per cent of iodine in such a combination.

Drug Therapy of Hyperthyroidism. The fact that certain groups of sulfur-containing compounds will on repeated administration lead to enlargement of the thyroid and to hypothyroid symptoms was first demonstrated in 1942 by three groups of scientists, working independently. The hypothyroidism produced by such compounds was shown to be due to an interference with the formation of thyroxine by inhibiting the conversion of inorganic iodide to thyroxine and thyroxin. The thyroid enlargement was shown to result from stimulation of the thyroid by the thyrotropic hormone of the anterior pituitary in response to the reduction in thyroid activity, a condition which has been described as "hyperplasia of frustation." The clinical significance of such drugs for the treatment of hyperthyroidism was immediately realized and *thiouracil* was found to be the best suited of the available compounds for therapeutic purposes.

While *thiouracil* represents a considerable advance in the therapy of hyperthyroidism, it is a toxic agent and has caused a number of deaths. The most severe toxic effect is the occasional development of agranulocytosis. Less severe reactions include gastro-intestinal disturbances, edema of the legs, enlargement of the submaxillary glands, jaundice and skin rashes. Search is continuing for a less toxic drug than *thiouracil*, 6-propyl *thiouracil* being one of the more promising compounds.

It was early suggested that thyroxin in nature is derived from tyrosin and di-iodotryosine. Support for this hypothesis has been given by the studies of Chaikoff and his associates with radioactive iodide. These workers reported that when radioactive iodide was introduced into the body, subsequent analyses of the thyroid showed it to be distributed in the inorganic iodide, di-iodotryosine and thyroxin fractions respectively, the amount present in the thyroxin fraction becoming progressively greater as the time interval increased.

The formation of thyroxin is probably not confined to the thyroid gland since studies with radioactive iodide have shown thyroxin may be formed in completely thyroidectomized animals. Thyroxin has been produced in vitro not only by adding iodine to blood proteins, but also to other proteins rich in tyrosine, such as casein. Increasing the iodination of casein until the iodine content is about 7 per cent causes an increasing physiologic activity in the preparation. However, when the iodine content is further increased, the physiologic activity is decreased.

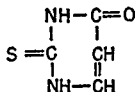
**Therapeutic Use.** Thyroid preparations are used almost entirely for the treatment of hypothyroidism. The usual form of medication is by tablets of desiccated glands administered orally. Thyroxin itself has little or no clinical application. It is not used orally because of the unpredictability of its absorption and although, unlike crude thyroid preparations, it can be given intravenously, this route is rarely if ever indicated. Patients under thyroid treatment should be observed closely for the development of hyperthyroid symptoms, which include nervousness, tachycardia and loss of weight. The maximal effects of thyroid therapy are not obtained until several weeks after institution of therapy.

Thyroid extracts have been used in the treatment of obesity and also to produce an increased sense of well-being. Because of the dangers of hyperthyroidism, however, their use for these purposes is dangerous except under strict

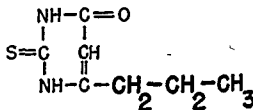
dental removal of the glands during thyroidectomy. The condition is characterized by a lowering of the serum-calcium level, a rise in the inorganic phosphate level and a decrease in phosphate excretion. The symptoms include increased neuromuscular excitability leading to tetany, brittleness of the skin, dryness of the hair, formation of cataracts and occasionally cardiac disturbances and psychoses.

A parathyroid extract capable of combating the effects of parathyroid insufficiency was first prepared by Collip in 1925. The active principle frequently referred to as *parathormone* has not been isolated, though chemical studies indicate it to be of protein nature. Its physiologic action has been variously explained as being due either to an increased mobilization of calcium from the bones or to an increase in the excretion of phosphate by the kidney leading indirectly to a rise in blood calcium. Convincing experimental evidence has been presented in support of both arguments and it may well be that a dual effect is involved. Parathyroid extracts are of limited value in the treatment of hypoparathyroidism because tolerance develops after some weeks and the hypocalcemia is no longer affected. Furthermore, parathormone is inactive by mouth, being destroyed by the digestive juices. For prolonged treatment of hypoparathyroidism or other hypocalcemic conditions, activated steroids must be used. The value of these preparations was first demonstrated by Holtz, in Germany, in 1933. The most widely used compound is *dihydroxycholesterol*, also known as A.T. 10 (antitetanic compound No. 10), which is closely related chemically to calciferol (vitamin D<sub>2</sub>) but which has little or no antitetrachitic activity. Vitamin D preparations can also be used to maintain the blood-calcium level but large doses are required. The activated steroids can be given by mouth. Their action develops slowly, however, and parathormone must be used in acute tetany. It is frequently supplemented with intravenous injections

Thiouracil has been used in the treatment of hyperthyroidism when operative relief is not feasible or desirable. It will not relieve exophthalmic conditions; in fact, since such conditions are believed to be caused by the thyrotropic hormone, they may conceivably be aggravated by thiouracil. Thiouracil can be used for preoperative treatment in thyroidectomy, especially in patients who do not respond to or who do not tolerate iodides. It does not produce such a desirable operative field as iodides, however, since it causes a hyperemia and softening of the gland. The full effects of thiouracil may require several weeks of treatment as it does



Thiouracil



6-Propylthiouracil

not affect the stores of thyroxin in the body but only the formation of additional thyroxin.

Recently, radioactive iodide has been used in the treatment of hyperthyroidism and adenocarcinoma of the thyroid. Because of the affinity of the thyroid for iodide, the radioactive material becomes concentrated in the gland and effects an internal radiation. Toxic reactions are similar to those of acute roentgen-ray sickness and include nausea, vomiting, malaise and fever.

## PARATHYROIDS

The internal secretion of the parathyroid gland plays an important role in the metabolism of calcium and phosphorus. The exact nature of its action is not, however, fully understood. Hypoparathyroidism may occur idiopathically or can be ascribed definitely to disease or to acci-

No definite endocrine function has been determined for the thymus gland. It has long been known that some myasthenia gravis patients have characteristic tumors in the thymus known as thymomas. Recently, surgical removal of the thymus has been reported to afford some measure of relief to these patients. This has led to the suggestion that the thymus gland is in some way related to the metabolism of acetylcholine in the body.

## THYMUS

## PREPARATIONS

Posterior-pituitary injection U.S.P.; pituitary (posterior lobe) extract B.P. Aqueous extract containing 10 units per cc. 0.2-2 cc.  
 Ampuls pitocin N.N.R. Contain 10 oxytocic units per cc. 0.3-1 cc.  
 Ampuls pitressin N.N.R. Contain 20 pressor units per cc. 0.3-1 cc.  
 Pitressin tannate in oil N.N.R. 5 pressor units per cc. 0.3-1 cc.  
 Insulin injection U.S.P. Contains 40, 80 or 100 U.S.P. insulin units per cc.  
 Injection of insulin B.P. 20, 40 or 80 units per cc.  
 Protamine zinc insulin N.N.R. 40 or 80 units per cc.  
 Protamine zinc insulin injection U.S.P.; B.P. 40 or 80 units per cc.  
 Zinc insulin crystals N.N.R. Contain not less than 22 units per mg.

Crystalline zinc insulin injection N.N.R.

Globin insulin with zinc N.N.R. 40 or 80 units per cc.  
 Thyroid U.S.P. Contains not less than 0.17 per cent or more than 0.23 per cent iodine in thyroid combination and must be free from iodine in inorganic or any form of combination other than that peculiar to the thyroid gland. 60 mg. Thyroid tablets U.S.P. Usually in 15, 30, 60 and 120 mg. amounts.



of calcium gluconate or chloride. During the treatment of parathyroid deficiency, the serum calcium must be followed until a stable level is reached in order to detect the development of hypercalcemia, which may cause serious if not fatal damage.

**Hyperparathyroidism.** This may result either from adenoma or hypertrophy of the parathyroids or from overdoses of parathormone. Symptoms include muscular weakness and pathologic changes in the bones, due to a withdrawal of calcium. The serum-calcium level is very high and the serum-phosphorus level low unless kidney damage is present. Increased amounts of calcium and phosphates are excreted in the urine, which may result in formation of urinary calculi or deposition of calcium in the pyramids leading to renal insufficiency.

**Standardization of Parathyroid Extracts.** The U.S.P. unit of parathyroid activity is equivalent to one one-hundredth of the amount required to raise the calcium content of 100 cc. of the blood serum of normal dogs 1 mg. within 16 to 18 hours after administration.

### LIPOCAIC

The depancreatized animal undergoes characteristic fatty changes in the liver that eventually lead to death despite the administration of insulin. These changes can be prevented by the addition of raw pancreas to the diet. Dragstedt and his associates have prepared a fat-free extract of the pancreas, which exerts the same effect as fresh pancreas in daily doses of from 60 to 100 mg. These investigators believe the effect is of an endocrine nature and have designated the active principle *lipocaic*. Preliminary clinical trials indicate this preparation may be of value in disturbances of fat metabolism in diabetic patients. Clinical experience is not sufficient, however, to indicate whether lipocaic has a place in the treatment of human disease.

# INSULIN

- Abel, J. J., E. M. K. Gelling, C. A. Rouiller, F. K. Bell and O. Wintersteiner: Crystalline insulin, *J. Pharmacol. & Exper. Therap.* 31: 65, 1927.
- Adlersberg, D., and H. Dolger: Insulin mixtures in the treatment of diabetes: variable versus fixed ratios of insulin and protamine zinc insulin, *J.A.M.A.* 128: 414, 1945.
- Bailey, O. T., C. C. Bailey and W. H. Hagan: Alloxan diabetes in the rabbit: a consideration of morphologic and physiologic changes, *Am. J. M. Sc.* 208: 450, 1944.
- Banting, F. G., and C. H. Best: The internal secretion of the pancreas, *J. Lab. Clin. Med.* 7: 251, 1922.
- Brunschwig, A., J. G. Allen, F. M. Owens, Jr., and T. F. Thornton: Alloxan in the treatment of insulin-producing islet-cell carcinoma of pancreas, *J.A.M.A.* 124: 212, 1944.
- Brush, J. M.: Initial stabilization of the diabetic child, *Am. J. Dis. Child.* 67: 429, 1944.
- Eaton, J. C.: Clinical trial of globin insulin and other insulins with delayed action, *Lancet* 2: 269, 1944.
- del Piombo, R. S., and E. L. Sevringhaus: Clinical use of new types of modified protamine zinc insulin, *Ann. Int. Med.* 22: 667, 1945.
- Goldner, M. G.: Insulin lipohypertrophy, *J. Clin. Endocrinol.* 3: 469, 1943.
- Greco, J. B., A. O. Lima and J. R. Cançado: The treatment of underweight with insulin, *Am. J. M. Sc.* 204: 258, 1942.
- Hagedorn, H. C., B. N. Jensen, N. B. Krarup and I. Wodstrup: Protamine insulinate, *J.A.M.A.* 106: 177, 1936.
- Martin, W. P., H. E. Martin, R. W. Lyster and S. Strouse: Insulin resistance—critical survey of the literature with the report of a case, *J. Clin. Endocrinol.* 1: 387, 1941.
- Reiner, L., E. H. Lang, J. W. Irvine, Jr., W. Peacock and R. D. Evans: The absorption rates of insulin, globin insulin and protamine zinc insulin labelled with radioactive iodine, *J. Pharmacol. & Exper. Therap.* 78: 352, 1943.
- Ricketts, H. T.: Certain aspects of the newer insulins, *Illinois Med. J.* 87: 133, 1945.

Thyroid B.P. Contains 0.1 per cent iodine in combination as thyroxine (limits 0.09–0.11) and not more inorganic iodine than 10 per cent of the content of total iodine.

Thyroxin U.S.P. 0.5 mg. intravenously.

Thyroxine sodium B.P. 0.1–1 mg.

Thyroxin fraction N.N.R. Partially purified disodium salt of thyroxin. For oral administration only.

Parathyroid injection U.S.P. Each cc. must contain a potency of not less than 100 U.S.P. units. 25 U.S.P. units intramuscularly.

#### POSTERIOR PITUITARY

Adler, F. H., and P. R. McDonald: Studies on pigmentary degeneration of the retina: the rôle of the melanophore hormone of the pituitary gland in pigmentary degeneration of the retina, *Tr. Am. Ophth. Soc.* 39:49, 1941.

Blotner, H.: Pitressin tannate in oil in the treatment of diabetes insipidus, *J.A.M.A.* 119:995, 1942.

Court, D., and S. Taylor: Slowly acting pituitary preparations in diabetes insipidus, *Lancet* 1:265, 1943.

Fisher, C., W. R. Ingram and S. W. Ranson: Diabetes insipidus and the neuro-hormonal control of water balance; a contribution to the structure and function of the hypothalamico-hypophyseal system, *Ann Arbor, Mich., Edwards*, 1938.

Geiling, E. M. K., and F. K. Oldham: The site of formation of the posterior lobe hormones, *Tr. A. Am. Phys.* 52:132, 1937.

Greene, J. A., and L. E. January: Efficacy of pellets of posterior hypophysis and of pitressin in oil in diabetes insipidus, *Proc. Soc. Exper. Biol. & Med.* 44:217, 1940.

Jones, G. M.: Diabetes insipidus—clinical observations in forty-two cases, *Arch. Int. Med.* 74:81, 1944.

Pickford, M.: Control of the secretion of antidiuretic hormone from the pars nervosa of the pituitary gland, *Physiol. Rev.* 25:573, 1945.

Smith, B., Jr., J. M. Coon, P. Fourt and E. M. K. Geiling: A proposed modification in the official method for the assay of posterior pituitary solution, *J. Am. Pharm. A.* 30:151, 1941.

# Vitamins

VITAMIN A	VITAMIN E
VITAMIN B COMPLEX	VITAMIN P
VITAMIN C	VITAGENS
VITAMIN D	PREPARATIONS

Vitamins are protective agents which are required for normal growth and reproduction and whose deficiency leads to characteristic clinical symptoms which can be alleviated by administration of the deficient vitamin. They differ from the hormones in that they are of exogenous origin, the body's needs being normally supplied by ingestion of the active principles or their precursors.

Vitamins evoke few pharmacologic effects other than alleviation of symptoms characteristic of deficiency of the vitamin in question. They are effective in relatively small amounts. The symptoms of hypervitaminosis are not as apparent as those of excess hormone formation or administration; most preparations are comparatively nontoxic even in high dosage.

It should be borne in mind that vitamins have been greatly exploited by commercial interests and that the ideal source of vitamins is an adequate diet. Vitamin preparations should, therefore, be used only where prompt relief of hypovitaminosis is indicated, when demand for vitamins is increased, or where conditions necessitate a restriction of the diet. Indiscriminate use of vitamins should be dis-

Weitz, M. A.: Insulin hypersensitivity with desensitization—report of a case, *J. Allergy* 14:220, 1943.

### THYROID

Chapman, E. M. and R. D. Evans: The treatment of hyperthyroidism with radioactive iodine, *J.A.M.A.* 131:86, 1946.

Harrington, C. R.: The thyroid gland—its chemistry and physiology, New York, Oxford, 1933.

Harrington, C. R.: Thyroxine; its biosynthesis and its immunochemistry, *Proc. Roy. Soc., London*, 132:223, 1944–1945.

Reineke, E. P., and C. W. Turner: The recovery of crystalline thyroxine from iodinated casein, *J. Biol. Chem.* 149:555, 1943.

Soskin, S., and R. Levine: Recent advances in physiology of the thyroid and their clinical application, *Arch. Int. Med.* 74:375, 1944.

Williams, R. H.: Thiouracil treatment of thyrotoxicosis, I, the results of prolonged treatment, *J. Clin. Endocrinol.* 6:1, 1946.

Williams, R. H., H. M. Clute, T. J. Anglem and F. R. Kenney: Thiouracil treatment of thyrotoxicosis, II, toxic reactions, *J. Clin. Endocrinol.* 6:23, 1946.

### PARATHYROIDS

Shelling, D. H.: The Parathyroids in Health and in Disease, St. Louis, Mosby, 1935.

Rose, E.: Hypoparathyroidism. *Clinics*, 1:1179, 1943.

Sevringhaus, E. L.: Activated sterols and calcium salts in the treatment of parathyroid tetany, *Am. J. M. Sc.* 203:726, 1942.

### LIPOCAIC

Dragstedt, L. R.: Some physiologic problems in surgery of the pancreas, *Ann. Surg.* 118:576, 1943.

### THYMUS

Blalock, A., A. M. Harvey, F. R. Ford and J. L. Lilienthal, Jr.: The treatment of myasthenia gravis by removal of the thymus gland, preliminary report, *J.A.M.A.* 117:1529, 1941.

thyroidism, and vitamin K preparations as coagulants. The mode of action of none of the vitamins is fully understood. Some vitamins are known to be an essential component of certain enzymes; others may act as "promoters" of enzymatic reactions.

The importance of vitamins to the growth and development of micro-organisms and of malignant growths should not be overlooked. There is evidence to indicate that certain diseases may be limited by vitamin deficiencies or encouraged by the presence of certain vitamins.

Certain other protective agents are recognized whose effect on normal growth and development is as essential as that of the vitamins. These substances have been variously described as vitamins, dietary factors or vitamins and include choline, inositol, certain fatty acids and the essential amino acids. As yet the therapeutic application of these substances is largely experimental, but as knowledge of their metabolism is advanced, they will undoubtedly come to play as important a role as the vitamins.

Vitamins for therapeutic purposes are supplied as crude extracts or as synthetic preparations which may be either identical with the natural vitamin or which may possess vitamin-like activities. Preparations of known composition can be assayed by chemical or physical methods. Others are assayed biologically. The older biologic assay methods are based on the use of laboratory animals depleted of the vitamin to be assayed. When deficiency symptoms appear, the preparation to be assayed is added to the deficient diet and its efficacy in restoring the health of the animal is compared to that of a standard preparation in similarly prepared animals. Recently the nutritional requirements of certain micro-organisms have been shown to provide a sensitive method of assay that can be completed rapidly and that involves the use of only minute amounts of the active principles. A number of these methods have been adopted by the U.S.P.

couraged. There is evidence that excess of one vitamin may lead to an increased requirement for a second, although the interrelationship between the vitamins is as yet poorly understood. Combinations of vitamins or crude preparations are often more efficacious than individual vitamins since rarely does a deficiency in a single vitamin exist. The use of preparations of vitamin B complex in particular is usually more desirable than the use of a single crystalline vitamin belonging to the complex. Finally, it must be recognized that our knowledge of the vitamins is as yet incomplete and that unknown factors may be supplied in the relatively crude preparations.

Vitamins are prescribed either at supplementary or at therapeutic levels. Supplementary doses should be restricted to cases in which the diet is unavoidably inadequate or in which the vitamin requirements are increased as in pregnancy, lactation, fever or severe physical exertion. In such cases, multiple vitamin preparations such as hexavitamin tablets, dried yeast, crude liver preparations or rice polishings, containing approximately the daily requirement of various vitamins are given. Therapeutic doses of single or multiple vitamin preparations are usually from three to ten times the supplementary doses and are prescribed in cases of proven or suspected vitamin deficiency. The Federal Trade Commission has held to be misleading any therapeutic claims for supplementary levels of vitamins. Such dosages would be of value only in the very mildest of deficiency states and furthermore might tend to give the patient a false sense of security so that he may neglect a satisfactory diet. The range of dosage for supplemental and therapeutic levels of vitamins is set forth in Table 4.

This chapter is restricted, for the most part, to the discussion of the use of vitamins in well-recognized deficiency states. Reference is made elsewhere to the use of pteroylglutamic acid in macrocytic anemia, para-aminobenzoic acid in Rickettsial diseases, vitamin D preparations in hypopara-

relieving vitamin A deficiency. Signs of vitamin A deficiency which are relieved by the administration of the vitamin or one of its precursors include metaplasia of mucous epithelium, characteristic skin lesions, night blindness, and defects in tooth development in children. The use of vitamin A preparations in excess of normal requirements to reduce the incidence of respiratory or other infections is of no proven value.

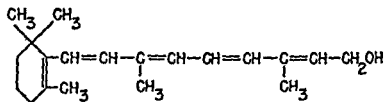
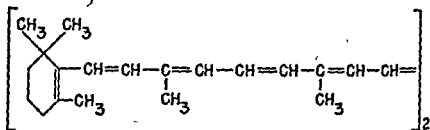
**Assay of Vitamin A Preparations.** Although vitamin A can be assayed spectrophotometrically, the official U.S.P. method of assay is a biologic one since it has been claimed that spectrophotometric methods can be influenced by adulteration. The British recognize both biologic and physical methods of assay but stipulate that the biologic method has priority if discrepancies exist between the two methods. The U.S.P. official method of bioassay for vitamin A consists of comparing the unknown preparation with a cod-liver oil preparation standardized for its vitamin A potency in regard to its ability to produce weight gains in rats rendered avitaminic by a vitamin A deficient diet (vitamin A test diet U.S.P.). The U.S.P. unit of vitamin A activity is identical with the International unit, being the specific activity of 0.6 micrograms of pure beta-carotene.

## VITAMIN B COMPLEX

The vitamin B complex includes a number of water-soluble vitamins, the richest sources of which include yeast and liver. It is probable this group contains many as yet unidentified protective agents. The substances identified to date vary greatly in their chemical structure and in their physiologic roles. They have all been prepared synthetically. The term vitamin B (antineuritic vitamin) was first applied to the water-soluble thermolabile principle isolated from rice polishings and yeast which alleviated the symptoms of beriberi. The isolation from similar sources of a second water-soluble principle which differed from vitamin B in



## VITAMIN A

 $\beta$ -Carotene

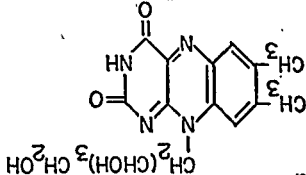
Vitamin A

Vitamin A is a fat-soluble vitamin, obtained commercially from fish-liver oil. The dietary sources of vitamin A include green, leafy and yellow vegetables, dairy products and liver. In plants and dairy products, the vitamin A activity is due largely to the presence of provitamins, particularly beta-carotene, which can be converted into vitamin A or stored in the body if there is no immediate need for additional vitamin A. Excessive intake of these substances or a failure of the liver to convert them to vitamin A may lead to carotinemia. While the condition is apparently harmless, the yellow tinting of the blood, skin and conjunctiva which accompanies it may be confused with jaundice. Animals given massive doses of vitamin A develop characteristic symptoms which include loss of weight, internal hemorrhages and fractures of the bones of the extremities. There is some evidence that hypervitaminosis A may occur in humans, though potent preparations are not as yet readily available.

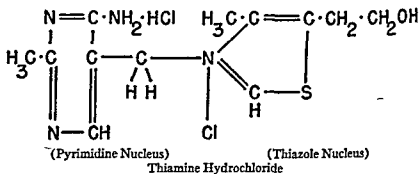
At present, there is no evidence that vitamin A preparations have any therapeutic action other than that of

after depletion has occurred. Any complicating conditions, such as pregnancy, illness or undue exertion, may, however, lead to mild symptoms of thiamine deficiency, such as general fatigue, loss of appetite, poor memory and muscle cramps, or to more severe symptoms, including degenerative changes in the nervous system, edema and cardiac hypertrophy. The term beriberi is usually reserved to describe these severe symptoms, which arise in the Orient due to the consumption of polished rice. Essentially similar clinical findings, however, are presented by the Korsakoff syndrome, alcoholic polyneuritis, Wernicke's disease and other polyneuritides due to faulty nutrition. These conditions may be treated with crystalline thiamine or with substances rich in vitamin B<sub>1</sub> which have the probable advantage of containing other members of the vitamin B complex, since it appears probable that other avitaminoses are also present. Thiamine is best administered orally. Fatal anaphylactic shock has occurred following its intravenous injection, and sensitivity may develop after prolonged parenteral use.

Standardization of Thiamine. The U.S.P. official method of assay for vitamin B<sub>1</sub> preparations involves the use of rats rendered polyneuritic by a test diet. Crystalline thiamine hydrochloride is the official standard preparation, 3 micrograms containing one unit of activity. Thiamine hydrochloride and other products from which certain interfering substances are absent may be assayed by a fluorometric procedure.



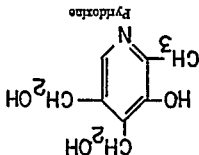
being thermostable and which relieved the symptoms of pellagra led to the separation of "water-soluble vitamin B" into two fractions, vitamin B<sub>1</sub> (thermolabile) and vitamin B<sub>2</sub> (thermostable). The subsequent discovery that vitamin B<sub>2</sub> consisted of not one but several substances led to the continued acceptance of vitamin B<sub>1</sub> for the antineuritic vitamin (later identified as thiamine) and the use of B<sub>2</sub>, B<sub>3</sub>, B<sub>4</sub>, etc., for additional activities as they were discovered. As the chemical structure of these compounds becomes established, and as synthetic preparations become available, they are generally referred to by their chemical names rather than as one of the B vitamins. Only those members of accepted therapeutic value are discussed in this section.



**Thiamine.** Thiamine or vitamin B<sub>1</sub> is of considerable historical interest since the demonstration of its antiberberi action led to the formulation of the present-day concept of vitamins. It was first isolated in crystalline form in 1926 by Jensen and Donath and its empirical formula determined by Windaus in 1932. Its structural formula and synthesis were reported by Williams and Cline in 1936. It is known in Europe as aneurin. Sources of thiamine include pork, dried yeast and rice husks. Live yeast contains much thiamine but the organisms apparently prevent its being available to man. The body does not store thiamine to any appreciable extent, although the appearance of deficiency symptoms may be delayed for several weeks or even months

be prejudicial to its use, hence the term niacin has been generally adopted. Nicotinic acid is probably present in the living animal in the form of its amide, nicotinamide. Nicotinic acid and nicotinamide are used mainly for the prevention and treatment of pellagra. Nicotinic acid frequently causes a disagreeable but not serious flushing of the skin of the face and neck and extremities. Nicotinamide does not produce the effect, although it is about twice as toxic to animals as nicotinic acid.

Standardization of Nicotinic Acid or Nicotinamide. The official U.S.P. method of assay for nicotinic acid and nicotinamide is a microbiologic procedure, using *Lactobacillus arabinosus* as the test organism and the U.S.P. Nicotinic Acid Reference Standard as a basis of comparison of activity.



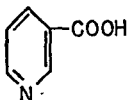
Pyridoxine. Pyridoxine (vitamin B<sub>6</sub>) was first isolated in 1938 by five different groups of workers. Its chemical structure was elucidated and its synthesis accomplished in 1939 by two groups of workers, one in Germany and one in the United States. It is widely distributed in nature, the main food sources being grain, egg yolks and milk.

The clinical value of pyridoxine has not been fully established. It appears to promote the recovery of pellagrins who are not completely cured with nicotinic acid and thiamine. It has recently been introduced for the prevention and the treatment of radiation sickness, the severity of which is believed by some investigators to be due to deficiencies of the vitamin B complex. Deficiency of pyridoxine

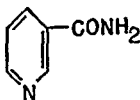
**Riboflavin.** Riboflavin, known also as vitamin G or lactoflavin, is widely distributed throughout the plant and animal kingdoms. The most important food sources include milk and meats. It was isolated in 1933 in three different laboratories, at which time its identity with lactochrome, a yellow, water-soluble, green-fluorescing pigment of whey, first investigated in 1879, was realized. Riboflavin was first synthesized in 1935 by Kuhn and Karrer.

Riboflavin is used in the treatment of riboflavin deficiency or "ariboflavinosis," the symptoms of which include glossitis, cheilosis and photophobia and other ocular disturbances. It is also used to treat the riboflavin deficiency in conditions in which multiple vitamin deficiencies undoubtedly exist, such as pellagra, black tongue and beriberi. No untoward effects have been reported following large doses of riboflavin.

**Standardization of Riboflavin.** A U.S.P. Riboflavin Reference Standard is available. Preparations are standardized by a microbiologic assay employing *Lactobacillus casei* as the test organism.



Nicotinic Acid



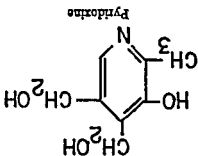
Nicotinamide

**Nicotinic Acid.** Nicotinic acid (niacin, antipellagra vitamin, P.P. [pellagra-preventing] factor) is the most important factor in the prevention of pellagra. Rich food sources of this vitamin include meats and whole wheat products.

Nicotinic acid was first prepared by the oxidation of nicotine in 1873, long before its vitamin activity was recognized. Its efficacy in curing black tongue and pellagra was demonstrated by Elvehjem and by Spies respectively in 1937. Although nicotinic acid is several hundred times less toxic than nicotine, it was felt the name association would

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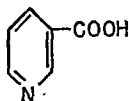


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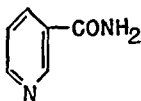
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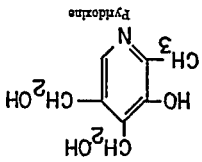
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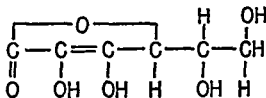
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in rats leads to "rat acrodynia" characterized by degenerative changes in the cardiac and striated muscles and changes in the nervous system. This has led to its use in such conditions as paralysis agitans and pseudohypertrophic muscular dystrophy, with promising results being reported in some cases.

### VITAMIN C



Ascorbic Acid

Vitamin C (ascorbic acid, cevitamic acid) is a water-soluble vitamin widely distributed in nature. The important food sources are fruits and vegetables, especially citrus fruits, tomatoes and potatoes. It is rapidly destroyed by heat and by oxidation. It was isolated from lemon juice by King and Waugh in 1932 and identified as the reducing compound "hexuronic acid" isolated earlier by Szent-Györgyi from the adrenal glands and vegetable sources. Its constitution was demonstrated and synthesis accomplished in 1933 by several workers. Synthetic vitamin C is now considerably more economical than that isolated from natural sources.

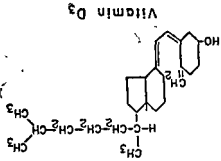
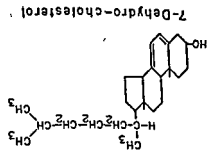
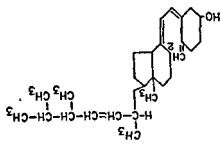
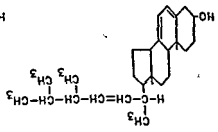
Ascorbic acid is the specific curative agent in scurvy, a condition due to a deficiency of this vitamin. It is probable that this disease is widespread in a subclinical or borderline form characterized by restlessness, irritability and general run-down feeling. More marked symptoms include capillary fragility, manifested by petechial hemorrhages in the skin and swollen and bleeding gums. The underlying pathology appears to be a change in the intercellular matrix of the connective tissue.

Adequate vitamin C is necessary to insure healing of bone fractures and wounds. However, there is no evidence that administration of vitamin C is of value if the body supplies are normal. It is said to have a detoxicant action on various toxic substances, such as lead and arsenic compounds, on bacterial toxins and on substances producing anaphylaxis.

Ascorbic acid can be administered orally or intravenously. It is apparently nontoxic even in large doses.

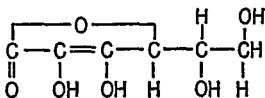
Standardization of Vitamin C Preparations. The U.S.P. unit of vitamin C is equivalent to the international unit and represents the activity of 0.05 mg. of the U.S.P. Ascorbic Acid Reference Standard. Preparations are assayed by chemical means based on the reducing ability of ascorbic acid. A biologic test is available, based either on the prevention or on the cure of scurvy in the guinea pig.

# VITAMIN D



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### VITAMIN C



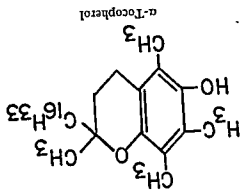
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calcification, especially in the kidneys and blood vessels. The use of vitamin D and activated sterols in the treatment of hypoparathyroid tetany is discussed in Chapter 21. Standardization of Vitamin D Preparations. The U.S.P. official method of assay of vitamin D preparations involves the use of rats given a rachitogenic diet. The preparations to be assayed are compared with the standard preparation in regard to their healing effect on the rachitic metaphysis by means of the "line test." In this procedure the leg bones are removed from the animal, cleaned and immersed in a silver-nitrate solution, which converts the calcium phosphate to silver phosphate. The criterion of healing is the presence of a new line of calcification through the rachitic metaphysis. The standard preparation is the U.S.P. Reference Cod-Liver Oil, standardized for its vitamin D potency. The U.S.P. and the international unit of vitamin D is equivalent to 0.025 microgram pure crystalline vitamin D<sub>2</sub>.

### VITAMIN E



Vitamin E is a fat-soluble vitamin widely distributed in foodstuffs. Commercially, it is available in concentrated form in wheat-germ oil or as synthetic alpha-tocopherol. No form of vitamin E deficiency has been established in human beings, a fact which has been attributed to its wide distribution and its unusual stability. In rats, vitamin E is

Vitamin D (antirachitic vitamin) consists of a group of fat-soluble substances which occur in physiologically active form only in animals. Plants contain "provitamins D," including ergosterol and 7-dehydrocholesterol, which can be converted into active vitamin D by ultraviolet light. Food sources of vitamin D include eggs, milk and milk products. Sunlight is an important factor in converting provitamins to an active form in the human or animal body, the skin providing a rich store of provitamins. Commercially, vitamin D is obtained from the liver oil of marine fishes, which is usually rich in both vitamins A and D, and by the irradiation of ergosterol or 7-dehydrocholesterol which yield vitamin D<sub>2</sub> (drisdol, calciferol, viosterol, activated ergosterol) or vitamin D<sub>3</sub> (activated 7-dehydrocholesterol) respectively. At least six different vitamins D are present in fish-liver oils. There appear to be quite marked differences in the responses of various species of animal to a given vitamin D and also in the response of a given species to various vitamins D.

Vitamin D preparations are used chiefly in the prevention and cure of infantile rickets, spasmophilia (infantile tetany), and osteomalacia or rickets of the adult, which occurs largely in pregnant and lactating women. These diseases result from faulty calcium and phosphorus metabolism due to vitamin D deficiency. The characteristic symptoms of these conditions are decalcification of the bone leading to brittleness and deformities and extreme muscular weakness. Large doses of vitamin D have been reported by several investigators to be of value in the treatment of lupus vulgaris. Vitamin D in massive doses has been recommended in the treatment of arthritis and has unfortunately been used quite widely in this condition without medical supervision. Its therapeutic value has been shown to be questionable, and numerous reports have appeared concerning the toxic effects of large doses of vitamin D, including gastro-intestinal upsets, weakness, skin eruptions and occasionally metastatic

Recently, a flavone glucoside, rutin, has been shown to have a much greater vitamin P activity than that of many of the available crude preparations. Rutin was first isolated in 1924 from tobacco but buckwheat has now been found to be a better source. Rutin is apparently nontoxic. It has been tried clinically in states of increased capillary fragility but as yet no verdict can be given concerning its therapeutic value.

## VITAGENS

Animal experiments have shown that choline, methionine, inositol and choline-containing phospholipids play an important role in the transport of fat from the liver. Deficiencies of these lipotropic factors lead to fatty infiltration and cirrhosis of the liver. Choline has been found to be particularly effective in reversing pathologic changes induced by choline deficiency which may follow, for example, a high intake of cystine while inositol is effective in combating changes induced by a high intake of cholesterol. These findings stimulated the therapeutic use of these lipotropic substances in liver disease in human beings, the most promising results having been obtained by the use of inositol and either choline or methionine.

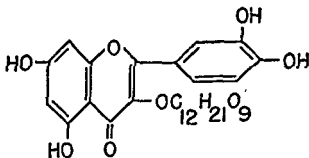
Fatty acids containing more than one double bond cannot be synthesized by the body. Since both linoleic and arachidonic acids are essential, they must be supplied in the diet. The amounts required are so small it is doubtful whether a deficiency is ever observed in man, with the possible exception of very young infants maintained on a low fat diet. In such instances, eczema may occur, apparently referable to a deficiency in the essential fatty acids. Certain amino acids must be included in the diet since their synthesis cannot be accomplished by the body. Specific deficiency of one or more of the essential amino acids is practically impossible when the total protein supply is adequate. One possible exception is arginine deficiency. A

essential to the processes of reproduction; in its absence, there is degeneration of the seminiferous epithelial cells in the male, and degenerative changes of embryos in the pregnant female, resulting in resorption of the embryos or in abortion. This has led to its use in the treatment of sterility and threatened or habitual abortion in human beings. Its value is questionable but its use has been justified on the grounds that it is nontoxic and that alternative treatment is usually ineffectual.

Laboratory animals on a vitamin E deficient diet develop nutritional muscular dystrophy and lesions of the nervous system. Consequently, vitamin E has been used in the treatment of muscular dystrophy and degenerative diseases of the nervous system. The results, however, have not been very encouraging, and all clinical uses of vitamin E must be considered only experimental at this time.

### VITAMIN P

Vitamin P has received little attention and not much is known as to its role as an essential nutritive element. It is present in citrus fruits and probably in many other plants. It appears to be a flavone derivative. Its physiologic action is concerned with maintenance of the walls of blood vessels and, in its absence, there is increased capillary fragility.



Rutin

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deficiency of this amino acid, produced experimentally in man, showed a specific effect on the production and motility of spermatozoa which was corrected by arginine supplements.

Recently, synthetic mixtures of the essential amino acids or of simple peptids and amino acids (casein digests or hydrolysates) have been used to provide the protein nitrogen requirements when normal feeding is interfered with. These preparations may be administered orally, intravenously or subcutaneously. Intravenous injection of hydrolysates occasionally causes febrile reactions or nausea and vomiting. The incidence of nausea and vomiting can be reduced by slow administration.

TABLE 4  
DAILY DOSE OF VITAMINS  
At Supplemental and Therapeutic Levels

VITAMIN	SUPPLEMENTAL LEVEL	THERAPEUTIC LEVEL
A	5,000 units	25,000-200,000 units
B <sub>1</sub> (thiamine)	1-2 mg.	20-100 mg.
B <sub>2</sub> (riboflavin)	2-3 mg	5-20 mg.
Nicotinic acid and nicotinamide	10-25	100-500
B <sub>6</sub> (pyridoxine)	?	5-10 mg.
C (ascorbic acid)	75	100-500 mg.
D	400 units	1,500-2,500 units
E (tocopherol)	?	30-100 mg.

## PREPARATIONS

(For dosage, see Table 4)

**Oleovitamin A, U.S.P.** Contains vitamin A from natural sources. Each gram contains not less than 50,000 or more than 65,000 U.S.P. units of vitamin A and not more than 1,000 U.S.P. units of vitamin D.

**Oleovitamin A capsules U.S.P.** Contain 5,000 or 25,000 U.S.P. vitamin A units per capsule.

Concentrated solution of vitamin A B.P. Contains 50,000 I.U. of vitamin A per gram.

Concentrated oleovitamin A and D U.S.P. Contains between 50,000 and 65,000 U.S.P. units vitamin A and between 10,000 and 13,000 U.S.P. units vitamin D per gram.

Oleovitamin A and D U.S.P. Contains between 850 and 1,100 U.S.P. units vitamin A and 85 and 110 U.S.P. units of vitamin D.

Concentrated oleovitamin A and D capsules U.S.P. Contain 5,000 U.S.P. units of vitamin A and 1,000 units of vitamin D per capsule.

Concentrated solution of A and D B.P. Contains 50,000 I.U. vitamin A and 5,000 I.U. vitamin D per gram.

Vitaminised oil B.P. Contains 1,000 I.U. vitamin A and 100 I.U. vitamin D per gram.

Emulsion of vitaminised oil B.P. Contains 50 per cent vitaminised oil.

Cod-liver oil U.S.P. Contains not less than 850 U.S.P. units vitamin A and 85 U.S.P. units vitamin D.

Cod-liver oil concentrate N.N.R. Contains between 50,000 and 65,000 U.S.P. units vitamin A and between 5,000 and 6,500 U.S.P. units vitamin D.

Cod-liver oil B.P. Contains not less than 600 units vitamin A activity and 85 units antirachitic activity.

Emulsion of cod-liver oil U.S.P.; B.P. 50 per cent emulsion of cod-liver oil U.S.P.; B.P.

Hallbut-liver oil U.S.P. Contains not less than 60,000 U.S.P. units of vitamin A and 600 U.S.P. units of vitamin D.

Hallbut-liver oil capsules U.S.P. Contain 5,000 or 25,000 U.S.P. units of vitamin A per capsule.

Hallbut-liver oil B.P. Contains not less than 30,000 units vitamin A and between 2,500 and 3,000 units vitamin D.

Burbot-liver oil N.N.R. Contains not less than 4,480 U.S.P. units vitamin A and 640 U.S.P. units vitamin D per gram.

Shark-liver oil N.N.R. Contains not less than 16,500 U.S.P. units vitamin A and 40 units vitamin D per gram.

- Percomorph-liver oil N.N.R. A mixture of fixed oils from various percomorph fish. Contains not less than 60,000 U.S.P. units of vitamin A and 8,500 U.S.P. units of vitamin D per gram.
- Carotene N.N.R.
- Carotene in oil N.N.R. Contains not less than 7,500 U.S.P. vitamin A units per gram.
- Liver—B-vitamins injection U.S.P. Each cc. contains not less than 0.08 mg. riboflavin, 0.5 mg. nicotinic acid and 12 mg. choline.
- Dried yeast U.S.P. Contains not less than 0.12 mg. thiamine hydrochloride, 0.04 mg. riboflavin and 0.25 mg. nicotinic acid per gram.
- Dried yeast tablets U.S.P.
- Triasyn B capsules and tablets U.S.P. Contain not less than 2 mg. thiamine hydrochloride, 3 mg. riboflavin and 20 mg. nicotinamide.
- Rice polishings U.S.P.
- Rice-polishings extract U.S.P. Contains not less than 20 U.S.P. units vitamin B<sub>1</sub>, representing approximately 14.5 Gm. rice polishings.
- Thiamine hydrochloride U.S.P. Aneurine hydrochloride B.P.
- Thiamine-hydrochloride tablets U.S.P. Available containing 3, 5 and 10 mg. thiamine hydrochloride.
- Thiamine-hydrochloride injection U.S.P.
- Adsorbate of vitamin B<sub>1</sub>; B.P. Contains 100 units antineuritic activity per gram.
- Nicotinic acid (niacin) U.S.P.; B.P.
- Nicotinic-acid tablets U.S.P. Available containing 25, 50 and 100 mg. nicotinic acid.
- Nicotinamide U.S.P.; B.P.
- Nicotinamide tablets U.S.P. Available containing 25 and 50 mg. nicotinamide.
- Nicotinamide injection U.S.P.
- Riboflavin U.S.P.; B.P.

- Riboflavin tablets U.S.P. Available containing 1 and 5 mg. riboflavin.
- Riboflavin injection U.S.P.
- Pyridoxine hydrochloride N.N.R. Accepted for purposes of standardization and experimentation only.
- Ascorbic acid U.S.P.; B.P.
- Ascorbic-acid tablets U.S.P.; B.P. Contains 25, 50 and 100 mg. ascorbic acid.
- Sodium-ascorbate injection U.S.P.
- Synthetic oleovitamin D (vitosterol in oil). Contains not less than 10,000 U.S.P. units of vitamin D per gram as either activated ergosterol or activated 7-dehydrocholesterol.
- Calciferol (vitamin D<sub>2</sub>) B.P. Contains 40,000 I.U. anti-rickets units per mg.
- Vitamin D<sub>2</sub> (Drisdol) N.N.R.
- Solution of calciferol B.P. Contains 3,000 I.U. per gram.
- Concentrated solution of vitamin D B.P. Contains 10,000 I.U. per gram.
- Hexavitamin tablets U.S.P. Each tablet contains not less than 5,000 U.S.P. units vitamin A, 400 units vitamin D, 75 mg. ascorbic acid, 2 mg. thiamine hydrochloride, 3 mg. riboflavin and 20 mg. nicotinamide.
- Amigen N.N.R. A hydrolysate of casein prepared by enzymatic digestion.
- Paranamine N.N.R. A hydrolysate of casein prepared by acid digestion.

## BIBLIOGRAPHY

## GENERAL

- The Biological Action of the Vitamins, A Symposium, Chicago, Univ. Chicago Press, 1942.
- Indiscriminate administration of vitamins to workers in industry, Council on Foods and Nutrition and the Council on Industrial Health, J.A.M.A. 118:618, 1942.
- The Vitamins—A Symposium, Chicago, A.M.A., 1939.

- Gordon, E. S., and E. L. Severinghaus: *Vitamin Therapy in General Practice*, Chicago, Yr. Bk. Pub., 1940.
- Methods of Vitamin Assay, New York, Interscience, 1947.
- Jeghers, H.: *Vitamins in present-day treatment*, M. Clin. North America 29:1294, 1945.
- Jolliffe, N.: The preventive and therapeutic use of vitamins, J.A.M.A. 129:613, 1945.
- Molitor, H.: *Vitamins as pharmacological agents*, Federation Proc. 1:309, 1942.
- Pett, L. B.: The use and abuse of vitamins, Canad. M. A. J. 52:488, 1945.
- Rosenberg, H. R.: *Chemistry and Physiology of the Vitamins*, New York, Interscience, 1942.

#### VITAMIN A

- Josephs, H. W.: Hypervitaminosis A and carotenemia, Am. J. Dis. Child. 67:33, 1944.
- Moore, T., and Y. L. Wang: Hypervitaminosis A, Biochem. J. 39:222, 1945.

#### THIAMINE

- Bean, W. B., T. D. Spies and R. W. Vilter: A note on irradiation sickness, Am. J. M. Sc. 208:46, 1944.
- Field, H., Jr., and W. D. Robinson: The absence of reactions following therapeutic doses of nicotinic acid amide, Am. J. M. Sc. 199:275, 1940.
- Laws, C. L.: Sensitization to thiamine hydrochloride, J.A.M.A. 117:176, 1941.
- Mann, I.: Ariboflavinosis, Am. J. Ophth. 28:243, 1945.
- Oppenheim, A., and B. Lih: Peroral administration of vitamin B<sub>6</sub> (pyridoxine hydrochloride) in the treatment of radiation sickness, Radiology 47:381, 1946.
- Reingold, I. M., and F. R. Webb: Sudden death following intravenous injection of thiamine hydrochloride, J.A.M.A. 130:491, 1946.
- Williams, R. R., and T. D. Spies: *Vitamin B<sub>1</sub> (thiamin) and its use in medicine*, New York, Macmillan, 1939.

## VITAMIN D

- Bauer, J. M., and R. H. Freyberg: Vitamin D intoxication with metastatic calcification, *J.A.M.A.* 130: 1208, 1946.  
Covey, G. W., and H. W. Whitlock: Intoxication resulting from the administration of massive doses of vitamin D with report of five cases, *Ann. Int. Med.* 25: 508, 1946.  
Gaumond, E., and J. Grandbois: Vitamin D<sub>2</sub> in the treatment of lupus vulgaris, *Canad. M. A. J.* 56: 205, 1947.

## VITAMIN E

- Mason, K. E.: Physiological action of vitamin E and its homologues, *Vitamins & Hormones* 2: 107, 1944.  
Minot, A. S., and H. E. Frank: Serum tocopherol—its relation to failure of vitamin E therapy for pseudohypertrophic muscular dystrophy, *Am. J. Dis. Child.* 67: 371, 1944.  
Shute, W., and E. Shute: The prevention of premature labour, *J. Obst. & Gynaec. Brit. Emp.* 52: 570, 1945.

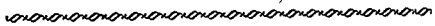
## VITAMIN P

- Griffith, J. O., Jr., J. F. Couch and M. A. Lindauer: Effect of rutin on increased capillary fragility in man, *Proc. Soc. Exper. Biol. & Med.* 55: 228, 1944.  
Scarborough, H.: Observations on the nature of vitamin P and the vitamin P potency of certain foodstuffs, *Biochem. J.* 39: 271, 1945.

## VITAGENS

- Beams, A. J.: The treatment of cirrhosis of the liver with choline and cystine, *J.A.M.A.* 130: 190, 1946.  
Best, C. H., and C. C. Lucas: Choline—chemistry and significance as a dietary factor, *Vitamins & Hormones* 1: 1, 1943.  
György, P.: Experimental hepatic injury, *Am. J. Clin. Path.* 14: 67, 1944.  
Hansen, A. E., and G. O. Burr: Essential fatty acids and human nutrition, *J.A.M.A.* 132: 855, 1946.  
Hecht, H. H.: Reactions to intravenously administered amino acids (casein hydrolysates), *Am. J. M. Sc.* 212: 35, 1946.

- Holt, L. E., and A. A. Albanese: Observations on amino acid deficiencies in man. *Tr. A. Am. Physicians* 58:143, 1944.
- Madden, S. C., S. H. Bassett, J. H. Remington, F. J. C. Martin, R. R. Woods and F. W. Shull: Amino acids in therapy of disease—parenteral and oral administration compared, *Surg. Obst. & Gynec.* 82:131, 1946.
- Riegel, C., C. E. Koop, R. P. Grigger, J. E. Rhoads and L. Bullitt: The protein requirements of surgical patients during the postoperative period, *S. Clin. of North America* 25:1096, 1945.



# Diagnostic Agents

PTHALATEIN DERIVATIVES  
RADIO-OPAQUE SUBSTANCES

BIOLOGIC PRODUCTS

PREPARATIONS

This chapter is devoted mainly to a discussion of various drugs used chiefly or wholly for securing information regarding the function and structure of various organs or tissues. It also includes a summary of a number of biologic products which are used to determine susceptibility to infectious diseases or to allergies.

To be of practical value, tests employing drugs for diagnostic purposes should be simple to perform and to interpret, and the agents used should not give rise to serious untoward reactions. Information concerning the techniques and the clinical value of the many liver- and kidney-function tests now in use may be found in the review articles which are listed in the bibliography.

## PTHALATEIN DERIVATIVES

In 1909, Abel and Rowntree examined a series of phthalateins with a view to finding a purgative suitable for subcutaneous injection. In the course of this work they reported that following parenteral administration phenoltetrachlorophthalatein was excreted only in the bile, while phenolsulfon-



phthalein (phenol red) was excreted almost exclusively in the urine. These findings were promptly adopted by Rowntree and his associates as a means of testing liver and kidney function respectively. Rowntree's liver-function test involved determination of the amount of the dye excreted in the stools during the 48-hour period subsequent to its intravenous injection. Rosenthal later showed that the liver function could be more conveniently tested by following the rate of disappearance of the drug from the blood stream. This investigator also examined a further series of phthalein dyes for their value in indicating hepatic damage and found that phenoltetrabromophthalein sodium sulfonate (sulfobromophthalein sodium U.S.P., bromsulphthalein) was the most suitable for the purpose.

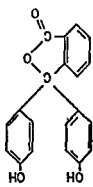
### PHTHALEINS

In 1923, Graham and his associates began a series of studies on radio-opaque bromo- and iodophenolphthalein derivatives which could be used simultaneously for cholecystography and for the determination of hepatic function. Of these, sodium tetraiodophenolphthalein (iodophthalein sodium U.S.P.) and sodium phenoltetraiodophthalein (phenetiophthalein sodium N.N.R.) are most commonly used.

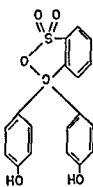
In general, the phenolphthalein compounds are relatively free from toxic symptoms. Sodium iodophthalein may cause gastro-intestinal upsets, dizziness and a fall in blood pressure. It should be used with caution in cases of heart and kidney damage.

Sodium fluorescein (sodium resorcinolphthalein) is used as a diagnostic agent in ophthalmology. It stains diseased areas of the cornea a bright fluorescent green, while foreign bodies appear in a green ring. Fluorescein has also been used to determine the line of demarcation of gangrenous areas. The dye is injected intravenously and areas with an adequate blood supply promptly show a greenish color under ultraviolet light.

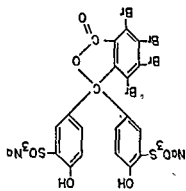
Phthaleins



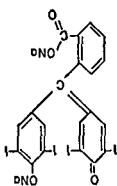
Phenolphthalein



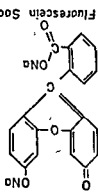
Phenolsulfonphthalein



Sulfobromophthalein Sodium



Iodophthalein Sodium



Fluorescein Sodium

## RADIO-OPAQUE SUBSTANCES

### BARIUM SULFATE

Barium sulfate was introduced in Germany in 1910 as a contrast medium for roentgen examinations of the gastro-intestinal tract. It is nontoxic because of its extreme insolubility and is very inexpensive. A number of fatal cases of barium poisoning have been reported due to accidental substitution of soluble salts, especially barium sulfide. To avoid such errors, it is recommended that when barium sulfate is prescribed, the title of the drug be written out in full.

Previous to the introduction of barium sulfate, insoluble bismuth salts were used in roentgen examination of the gastro-intestinal tract. They are still used to a limited extent, the subcarbonate being preferred to the subnitrate because of its lower toxicity.

### THORIUM DIOXIDE

Thorium dioxide is an intensely radio-opaque substance widely used as a contrast medium in the form of a stabilized colloidal solution (thorotrast). On intravenous injection, it is rapidly taken up by the cells of the reticulo-endothelial system and it is, therefore, of particular value in roentgenography of the liver, spleen and blood vessels. It has also been injected into the lacteal ducts in mammographic studies, but its use is accompanied with a high incidence of irritating effects.

The chief danger in the use of thorotrast lies in the fact that it remains in the body for an indefinite period of time, during which it emits radioactive disintegration products which may give rise to late toxic manifestations of a serious nature.

### IODINE PREPARATIONS

**Iodized Oils.** A number of radio-opaque preparations are available which consist of iodine addition products of vegetable oils. These preparations are nonirritating and can be

injected into various cavities of the body, such as the urinary and genital tracts, bronchi, fistulous tracts and the spinal canal. They are removed slowly from closed cavities and may give rise to foreign-body reactions. If injected under considerable pressure, oil embolism may result. The most common toxic symptoms associated with the use of iodized oils are those of iodism, including swelling of the parotid and submaxillary glands and skin eruptions. Allergic responses, occasionally fatal, have also been reported. *Pantopaque* was introduced in the United States in 1942 as a contrast medium in myelography. It consists of a mixture of isomeric esters, with ethyl iodophenylundecylic acid apparently the principal one. It is more fluid than the iodized oils and can be more readily injected into and aspirated out of the spinal arachnoid space.

**Water-Soluble Iodine Compounds.** In addition to certain phthalate compounds, a number of radio-opaque soluble organic iodine compounds are used for visualization of the urinary and biliary tracts. They should be avoided in renal or hepatic insufficiency, tuberculosis and other severe illness. Untoward effects occasioned by these preparations include flushing of the skin, nausea, skin eruptions and disturbances of respiration.

*Iopax* (uroselectan), *neo-iopax* (iodoxylum), *methiodal* (skiodan, abrodil), *iodypyracet* (diodrast, neo-skiodan) and *hippuran* are effective contrast substances for use in intravenous pyelography or for retrograde pyelography. The first of these substances to be used clinically was *iopax*, which was introduced for intravenous pyelography by Swick in 1929 to replace the more toxic sodium iodide introduced by Kownree and his associates in 1923. Large doses of these preparations may lead to suppression of urine formation. Iodopyracet is also used in roentgen examinations of the biliary tract and blood vessels. For the latter purpose, a concentrated solution is available. The technique, however, is quite complicated and not without danger.

## RADIO-OPAQUE SUBSTANCES

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## BIOLOGIC PRODUCTS

A number of biologic products are available for the diagnosis either of the presence of or the susceptibility to a given disease. A summary of the nature, source and usefulness of these preparations is presented in Table 5.

Other biologic products are used in diagnosis and treatment of hypersensitivity reactions. These include proteins from animal and plant sources, extracts of animal furs, feathers and hairs, and pollen extracts. None of these preparations has been recognized by the United States Pharmacopoeia. However, a number are listed in New and Non-official Remedies, from which further details can be obtained.

## PREPARATIONS

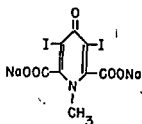
Sulfobromophthalain sodium U.S.P.  
Sulfobromophthalain-sodium injection U.S.P. Usually available 150 mg. sulfobromophthalain in 3 cc. I.V. 2-5 mg./Kg.  
Iodophthalain sodium U.S.P. Iodophthalain B.P. I.V. 0.3 Gm. per 10 Kg. Oral 0.5 Gm. per 10 Kg.  
Phenolsulfonphthalain (phenol red) U.S.P.  
Phenolsulfonphthalain injection U.S.P. Usually available as 6 mg. in 1 cc. I.V. or intramuscular 6 mg.  
Phenoltetrachlorophthalain N.N.R. I.V. 5 mg./Kg.  
Phentiotthalain sodium (phenoltetraiodophthalain Na) N.N.R. I.V. 40 mg./Kg.  
Fluorescein sodium U.S.P. Soluble fluorescein B.P.  
Iodized oil U.S.P. An iodine addition product of vegetable oils containing from 38 to 42 per cent combined iodine.  
Iodised oil B.P. Iodine addition product of poppyseed oil. Contains from 39 to 41 per cent combined iodine.  
Lipiodol 40 per cent iodine N.N.R.  
Lipiodol radiologique ascendant N.N.R. Contains 10 per cent iodine.

*Iodoalphionic acid* (priodax) was introduced in Germany in 1940 under the name of biliselectan as a medium for cholecystography. It is claimed to cause fewer gastro-intes-

### Iodine Compounds



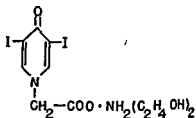
Iopox



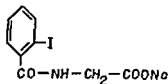
Neo-iopox



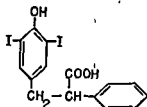
Methiodal sodium



Iodopyracet



Hippuran



Iodoalphionic acid

tinal upsets than iodophthalein. Furthermore, it is excreted largely by the kidneys and therefore does not cause confusing shadows in the hepatic flexure. Iodoalphionic acid is known in Great Britain as pheniodol.

Iodobrassicid N.N.R. Iodine addition product of rapeseed oil.  
 Iodopyracet injection U.S.P. Diodrast.  
 Iodoxyil B.P. Neo-iopax N.N.R. 15 Gm. in 20 cc. solution intravenous.  
 Hippuran N.N.R.  
 Methiodal sodium N.N.R.  
 Iodoalphonic acid N.N.R. 3 Gm.

BIBLIOGRAPHY  
 (Diagnostic Agents)

GENERAL

Eggleston, C., and H. Gold: Drugs used in clinical diagnosis—review of recent literature, *Am. J. M. Sc.* 208: 661, 1944.  
 Pearlmutter, M.: Drugs used in clinical diagnosis; II, Review of recent literature, *Am. J. M. Sc.* 212: 613, 1946.  
 Mater, J. G., J. I. Baltz, D. F. Marion, R. A. Holland and E. M. Yagle: A comparative evaluation of the newer liver function tests, *Am. J. Digest. Dis.* 9: 13, 1942.  
 McGhee, L. C., and J. E. Martin: Limitations of renal function determination, *Ann. Int. Med.* 132: 1626, 1940.  
 Tetelbaum, M., A. C. Curtis and S. M. Goldhamer: The comparative value of several liver function tests, *Ann. Int. Med.* 22: 653, 1945.  
 Weir, J. F.: Tests of liver function, *Mt. Clin. North America* 9743, 1945.

PTHALAIN DERIVATIVES

Abel, J. J., and L. G. Rowntree: On the pharmacological action of some phthaleins and their derivatives, with especial reference to their behavior as purgatives, *J. Pharmacol. & Exper. Therap.* 1: 231, 1909-1910.  
 Graham, E. A.: The story of the development of cholecystography, *Am. J. Surg.* 12: 330, 1931.  
 Hatfield, C. A., R. A. Byers and A. A. Wallking: Fluorescein—its use in determining the viability of strangulated intestine, *Surg. Gynec. & Obst.* 81: 530, 1945.  
 Rosenthal, S. M.: An improved method for using phenoltetrachlorophthalein as a liver function test, *J. Pharmacol. & Exper. Therap.* 19: 385, 1922.



TABLE 5  
BIOLOGIC TOXINS FOR IMMUNITY TESTS

PREPARATIONS	SOURCE	EFFECT OF INTRACUTANEOUS INJECTION
Diagnostic diphtheria toxin U.S.P.; (Schick test toxin)	<i>Corynebacterium diphtheriae</i> cultures.	Local skin reaction indicates susceptibility to diphtheria.
Scarlet fever streptococcus toxin U.S.P. (Dick test toxin)	Culture of suitable strains of hemolytic streptococci.	Local skin reactions indicate susceptibility to scarlet fever. Can be used in larger and repeated doses for active immunization.
Scarlet fever streptococcus antitoxin U.S.P.	Blood serum or plasma of healthy animal immunized against toxin produced by bacteria which cause scarlet fever.	Injection into site of rash will result in local disappearance of rash if due to scarlet fever. Can also be used to produce temporary passive immunity.
Old tuberculin U.S.P.; B.P. (Tuberculin-Koch) (Concentrated tuberculin) (Crude tuberculin)	Solution of growth products of culture of <i>Mycobacterium tuberculosis</i> .	Inflammation at site of injection indicates patient has been infected with tubercle bacilli at some time.
Purified protein derivative of tuberculin U.S.P. (P.P.D.)	As above, except nonprotein culture medium is used.	
Trichinella extract N.N.R.	Saline digest of <i>Trichinella larvae</i> .	Immediate or delayed local reaction indicates trichinosis.

# Local Anti-Infectives

24

INTRODUCTION	ACRIDINE DERIVATIVES
ALCOHOLS	PHENOLS
ACIDS	PREPARATIONS
DETERGENTS	HALOGENS
NITROFURAZONE	PEROXIDES
PREPARATIONS	

## INTRODUCTION

This chapter deals with a heterogeneous collection of preparations which are said to counteract infection when applied locally to the skin, mucous membranes and superficial wounds (antiseptics) or to inanimate objects (disinfectants). The activity of these preparations is due in some cases to a direct lethal effect on the pathogenic organisms (bactericides, germicides, fungicides or mycocides) and in others to an arresting of their growth or activity (bacteriostats, germistats, fungistats or mycostats).

The rational use of anti-infectives dates from the latter half of the nineteenth century. Pasteur's demonstration that putrefaction and fermentation were due to living microbes came to the attention of the British surgeon Lister, who was concerned with the high mortality from infection following surgical procedures. Stimulated by Pasteur's discoveries, Lister introduced the use of phenol to sterilize operating equipment, as a spray for decontamination of the atmosphere and as a wet dressing for wounds. Despite the dramatic results accomplished by these procedures, the irritat-

- Rosenthal, S. M., and E. C. White: Studies in hepatic function; VI-A. The pharmacological behavior of certain phthalein dyes, *J. Pharmacol. & Exper. Therap.* 24:265, 1925.
- Rowntree, L. G., and J. T. Geraghty: An experimental and clinical study of the functional activity of the kidneys by means of phenolsulphonephthalein, *J. Pharmacol. & Exper. Therap.* 1: 579, 1909-1910.
- Rowntree, L. G., S. H. Hurwitz and A. L. Bloomfield: An experimental and clinical study of the value of phenoltetrachlorophthalein as a test for hepatic function, *Bull. Johns Hopkins Hosp.* 24: 3277, 1913.
- Wirts, C. W., and A. Cantarow: A study of the excretion of bromsulphthalein in the bile, *Am. J. Digest. Dis.* 9: 101, 1942.

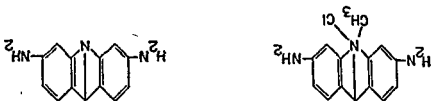
#### RADIO-OPAQUE SUBSTANCES

- Dangers of the injection of iodized oils—report of the Council on Pharmacy and Chemistry, *J.A.M.A.* 99: 1932, 1946.
- Bernstein, P.: Hysterosalpingography, a routine aid in gynecological diagnosis, *Am. J. Obst. & Gynec.* 48: 444, 1944.
- Eisen, D., and J. Goldstein: Lipiodol intravasation during uterosalpingography with pulmonary complications, *Radiology* 45: 603, 1945.
- von Lichtenberg, A.: The principles of intravenous urography, *J. Urol.* 25: 249, 1931.
- Mahon, G. S.: Reaction following bronchography with iodized oil, *J.A.M.A.* 130: 194, 1946.
- Reeves, D. L., and R. M. Stuck: Clinical and experimental results with thorotrast, *Medicine* 17: 37, 1938.
- Quinby, W. C., and G. Austen: Suppression of urine complicating pyelography, *New England J. Med.* 221: 814, 1939.
- Spier, J., L. W. Cluff and W. D. Urray: Aplastic anemia following administration of thorotrast, *J. Lab. & Clin. Med.* 32: 147, 1947.
- Unfug, G. A.: A comparative clinical investigation of cholecystographic preparations, *Radiology* 46: 489, 1946.
- Weber, H. M.: The present status of contrast myelography, *Am. J. M. Sc.* 206: 678, 1943.
- Yater, W. M., and F. O. Coe: Ten years' experience with thorotrast hepatosplenography, *Ann. Int. Med.* 18: 350, 1943.

is only reliable in determining the efficacy of water-soluble compounds related chemically to phenol. It is performed on a synthetic medium, using *Staphylococcus aureus* (or occasionally *E. typhosa*) as the test organism. Hence it does not take into account the effect of the presence of organic matter, nor does it yield information concerning the irritant effects of the compound on normal tissues. Several other methods have therefore been devised to obtain a broader range of information. These include toxicity studies on tissue culture cells or on chick embryos; determination of inhibiting effects on the respiration of liver tissue in vitro or on the phagocytic activity of leucocytes; and the examination of skin washings for the presence of bacteria following application of the preparation.

As yet, no ideal antiseptic has been developed. Such a substance should possess high efficiency and low toxicity. It should be capable of penetrating into skin, pus, cellular debris, and so on. It should not irritate, blister or burn the normal tissue nor should it interfere with the natural healing processes. Finally, it should be effective against a wide range of pathogenic organisms.

### ACRIDINE DERIVATIVES



2,8-diamino-10-methylacridinium chloride

2,8-diaminoacridine

Acridavine was first thought to be 2,8-diamino-10-methylacridinium chloride. It is now known to consist of a variable mixture of this compound and 2,8-diaminoacridine. Acridavine was shown by Ehrlich in 1912 to be trypano-

ing properties of phenol led to the abandonment of its use and to its replacement by aseptic technics. The interest in antiseptics was revived during World War I, when it became necessary to treat an overwhelming number of severely infected wounds under field conditions. After the war, however, interest in these preparations was negligible, in large part because of disappointing results following the earlier extravagant claims.

With the introduction of the sulfonamides and the antibiotics, it appeared that, at last, the problem of local antisepsis had been solved. Unfortunately, however, as a result of the widespread and often indiscriminate local use of these agents occasioned by the war, the inadequacies and dangers of the local use of the sulfonamides and also of penicillin soon became apparent (see Chapters 29 and 30). This led to a re-examination of the older preparations, especially of the acridine derivatives, and to a search for new preparations, of which propamidine seems the most promising (see Chapter 31).

The efficacy of antiseptics and germicides is greatly influenced by the conditions under which they are used. Important factors include the concentration of the drug; the duration of exposure and the nature of the solvent; the species of organism; the phase of its growth and the presence of serum, pus or blood. Thus, young cells are usually more susceptible than old ones, while spores or capsulated forms are, as a rule, very resistant. Organic substances, especially proteins, may lead to protective films around the organisms or to interference with the antiseptic. However, the activity of acriflavine, for example, may be increased by the presence of serum because of the fact that the dye is a more effective antiseptic in an alkaline medium.

The strength of an antiseptic or of a disinfectant is conventionally expressed by its phenol coefficient. This represents the ratio of its germicidal power to that of phenol, both being tested under identical conditions. The test, however,

## MERCURY AND SILVER PREPARATIONS

Inorganic Mercury Compounds. In 1881, Koch reported that solutions of mercuric bichloride possessed a powerful germicidal activity, destroying even bacterial spores. Although Geppert, in 1889, demonstrated conclusively that this preparation was bacteriostatic rather than bactericidal, Koch's views persisted and mercury compounds have long received an undeserved popularity as sterilizing agents. The value of mercurials as disinfectants and antiseptics is limited by their corrosive effect on metals, their irritant effect on tissues, their inactivation by organic matter and their high toxicity to man and animals. Of the inorganic preparations, only the soluble salts of the bivalent form are effective. The bichloride (corrosive sublimate) has been most widely used. Other preparations include the cyanide and the iodide.

The action of inorganic mercurials is thought to be due to the precipitation of the bacterial proteins by mercury ions with the formation of a mercury proteinate. The combination is believed to take place at the sulphydryl groups. Organic Mercury Preparations. Organic mercury compounds are less toxic and less effective anti-infectives than the inorganic mercury compounds. They are of some value when applied prophylactically to fresh wounds and are widely used as preservatives in biologicals which are to be administered parenterally. It should be emphasized, however, that neither inorganic nor organic mercury preparations are able to destroy spores. The action of organic mercurials may be due to the action of the molecule as a whole rather than to the liberation of mercurial ions. Organic mercurials used as anti-infectives include the phenyl mercuric compounds (borate, picrate and nitrate), merbromin (mercurochrome), nitromersol (metaphen) and merthiolate. Merbromin was introduced in 1919 by Young and his associates as a germicide for the genitourinary tract.

cidal, hence it is also known as tryptaflavine. Its bacteriocidal action was demonstrated by Browning in 1913 and it became widely used for wound antisepsis in World War I. It is probably the least effective and the most toxic of the acridine derivatives in present-day use.

Proflavine is 2,8-diaminoacridine. It was first made available as the bisulfate salt, which required neutralization with sodium bicarbonate or a buffering salt. It is now available as the less acid monosulfate. It has been used successfully as a fine dusting powder on suppurating wounds but should be used sparingly on relatively clean wounds, otherwise coagulation necrosis may be produced.

5-aminoacridine or monacrine was introduced by Albert in 1942. It has essentially the same properties as acriflavine and proflavine. It is almost colorless and does not therefore stain clothing. Both monacrine and diflavine (2,7-diaminoacridine) are said to be more effective against gram-negative organisms than the other acridines.

During World War II, the use of acridine dyes combined with sulfonamides was advocated because of their alleged synergistic action. However, such preparations, when used locally, owe their activity almost entirely to their acridine component and at the same time present the same hazards as does the local application of the sulfonamides.

The acridines inhibit the growth of a wide variety of pathogenic bacteria. They are active in the presence of serum proteins and are relatively nonirritant in effective concentrations, though high concentrations may have damaging effects on normal tissues. They possess a low systemic toxicity and probably do not interfere with phagocytosis. They have been injected intravenously as systemic anti-infectives but their value is questionable. Their disadvantages include their affinity for fabrics, such as surgical dressings and clothing and the instability to light of the colored compounds.

germicides and irritants than the strong preparations. They are used in concentrations of from 5 to 50 per cent.

## HALOGENS

Compounds liberating chlorine by hydrolysis, organic compounds containing highly active chlorine groups, and solutions of gaseous chlorine are germicidal, probably both by the formation of chloramines by replacement of the hydrogen in free amino groups of the bacterial proteins and by an oxidizing action. These preparations are used in the purification of water or sewage, in the disinfection of dairy equipment and for bleaching purposes. The more stable preparations, such as Dakin's solution (alkaline solution of sodium or potassium hypochlorite) and the chloramines, can be applied to infected wounds.

Iodine and certain iodine-containing compounds are widely used as antiseptics and disinfectants. Tincture of iodine is used almost routinely as a skin antiseptic at the site of surgical operations. Iodine-containing compounds, such as iodoform and iodochlorhydroxyquinoline (violet), have been used on wounds in the form of dusting powders. They liberate iodine slowly and lack the irritant action of tincture of iodine. The use of iodine preparations as amebicides is discussed in Chapter 26.

## PEROXIDES

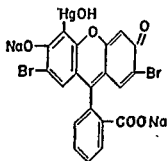
Hydrogen peroxide has a mild germicidal action due to the liberation of oxygen. This is greatly accelerated by the presence of organic matter and by the enzyme catalase, which is present in all living cells. The rapid evolution of gas makes the injection of hydrogen peroxide into closed cavities or abscesses dangerous.

Zinc peroxide consists of a mixture of zinc peroxide, zinc carbonate and zinc hydroxide. Like all metallic peroxides, it liberates oxygen more slowly than does hydrogen

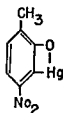


Its popularity immediatly became widespread and it was even used intravenously for the treatment of septicemia. Later, more critical studies showed its value to be quite limited.

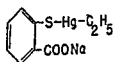
**Simple Silver Salts.** Silver salts, such as the nitrate, lactate and picrate, are astringent and corrosive as well as antiseptic and germicidal. Their activity is due largely to the liberation of silver ions and possibly to the liberation



Merbromin



Metaphen



Merthiolate

of silver, which is germicidal in very minute amounts. Silver nitrate as a 1 to 2 per cent solution has been used prophylactically against gonorrheal ophthalmia neonatorum since 1881, when Credé demonstrated its value.

Prolonged use of any silver preparation may result in permanent pigmentation of the skin (argyria).

**Colloidal Silver Preparations.** Colloidal silver preparations lack the astringent and corrosive properties of the silver salts. They consist of indefinite mixtures of metallic silver, silver oxide and various silver-protein compounds. The strong silver-protein preparations, such as protargol, are intermediate in their germicidal action between the silver salts and the mild silver protein compounds. They contain 8 per cent silver and are used in concentrations of from 0.1 to 10 per cent. Mild silver-protein preparations contain from 19 to 23 per cent silver, but they are less active

Radical alteration of the hydrogen-ion concentration will effectively kill most micro-organisms. However, strong acids and alkalis are too corrosive to use on living tissues. Weak acids, such as boric, benzoic and salicylic acids, have mild antiseptic properties, due both to their effect on the pH of the medium and to a specific toxic action of the undissociated molecule. They are also of value in restoring the normal acidity of infected areas of the skin, thereby assisting the natural defense mechanisms. Salicylic acid has the added advantage of being a keratolytic agent, producing a slow and painless destruction of the epithelium which aids in the removal of deep infections. Thus Whitfield's ointment, used widely in fungus infections and ringworm, consists of a mixture of 3 per cent salicylic acid and 5 per cent benzoic acid in a bland base.

## ACIDS

The cresols are several times as germicidal as phenol itself and somewhat less toxic. They have a very disagreeable odor and are relatively insoluble in water. Their toxicity and local irritant action may be reduced by esterification. One such compound is the acetic-acid ester of metacresol, metacresylacetate or cresatin. It is used in pure form or diluted with oils or alcohol.

Hexylresorcinol was introduced by Leonard in 1927. It is used as an antiseptic in a 1:1,000 solution in glycerin and water (S.T. 37), and as an antihelmintic in solid form (see Chapter 25). Its germicidal effect is due in large part to its surface-tension-lowering effect.

produce local anesthesia of the exposed area. They also act on the central nervous system depression. They are readily absorbed from wounds, mucous surfaces and the intact skin and may give rise to systemic poisoning characteristic of central nervous system depression. They are germicidal concentrations and penetrate poorly. They are made objects. They are irritant when applied to tissues in spores and are used, for the most part, for sterilizing inani-

peroxide. It is of value in the treatment of infections caused by anaerobic organisms.

Sodium peroxide forms an alkaline and caustic solution with water. It is used largely by dentists as a bleaching agent. Incorporated into soap, it is used in the treatment of acne.

Potassium permanganate also exerts its antibacterial activity by oxidation. It has been used for wound dressings and for the treatment of gonorrhea but its staining qualities are undesirable. It can be used in the disinfection of water, but it imparts a disagreeable taste and the residual manganese compounds may produce toxic effects.

### ALCOHOLS

Ethyl alcohol is a fairly effective germicide because of its dehydrating, coagulating and cleansing action. The optimum concentration is 70 per cent by weight.

Isopropyl alcohol is a more powerful germicide than ethyl alcohol and has the further advantage of being a more efficient cleansing agent because of its lower surface tension and greater fat-solvent activity. It is most active in full strength and is not so corrosive for metal instruments as 70 per cent ethyl alcohol. Neither ethyl nor isopropyl alcohol is capable of destroying spores even after prolonged exposure.

Glycol vapors, particularly those of propylene and triethylene glycol, have recently been shown by Robertson and his associates to be effective germicides for the control of air-borne diseases. When suitable practical technics have been evolved for dispersal of the vapors and for the control of their concentration, they should prove useful in the disinfection of closed spaces, such as hospital rooms, school-rooms, barracks and theaters.

### PHENOLS

The phenols exert their germicidal activity by coagulation of bacterial proteins. They are effective against many

spores and are used, for the most part, for sterilizing inanimate objects. They are irritant when applied to tissues in germicidal concentrations and penetrate poorly. They are readily absorbed from wounds, mucous surfaces and the intact skin and may give rise to systemic poisoning characterized by central nervous system depression. They also produce local anesthesia of the exposed area.

Hexylresorcinol was introduced by Leonard in 1927. It is used as an antiseptic in a 1 : 1,000 solution in glycerin and water (S.T. 37), and as an anthelmintic in solid form (see Chapter 25). Its germicidal effect is due in large part to its surface-tension-lowering effect.

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## DETERGENTS

The detergents include the common soaps and the so-called synthetic detergents. They exert their anti-infective action in large part by the simple removal of the microorganisms. They lower the surface tension of the water, enabling it to surround and wash away the adhering organisms as well as grease and dirt particles. The removal of the grease and the softening of the film in which the organisms are embedded makes the emulsification and washing off easier. In addition to their cleansing action, the detergents possess in many cases a direct toxic action on the bacteria. This may be intensified by the addition of other germicides, such as mercuric chloride, but usually the concentration is too low to be of any value if the preparation is to remain nontoxic.

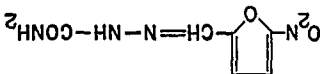
The action of the common soaps is enhanced by their content of free alkali and the appearance of considerably more alkali when the soaps are hydrolyzed. This alkalinity may be important in determining the degree of direct germicidal action of the soap. In addition, it promotes more rapid desquamation and thereby aids in the removal of pathogenic agents from the skin.

The most effective synthetic detergents are the cationic compounds, including benzalkonium chloride (zephiran chloride, a mixture of alkyl dimethyl benzyl ammonium chlorides), phemerol chloride and cetyl pyridinium chloride. These preparations consist essentially of ammonium salts with organic groups substituted for the hydrogen atoms. They are in general more effective against gram-positive than against gram-negative organisms. Their activity is greatly reduced by the presence of soap or other anionic detergents.

## NITROFURAZONE

It has been known for many years that a number of compounds containing the furan nucleus possess antiseptic properties. However, a systematic investigation of compounds

of this type was not undertaken until 1944, when Dadds and Stillman demonstrated that the presence of a nitro group at position 5 greatly increased the antibacterial activity. One such compound, 5-nitro-2-furaldehyde semicarbazone (nitrofurazone) has been recently introduced under the name of furacin as a dressing for wounds and chronic ulcers. It is apparently effective against both gram-positive and gram-negative organisms and is claimed to have little



## Nitrofurazone

or no effect on normal tissues. A number of cases of sensitivity have been reported following its use. These may well have been due to the ointment-like base in which the compound was incorporated and which has since been changed.

## PREPARATIONS

Acriflavine B.P. Acriflavine hydrochloride N.N.R. Usually used as 1:1,000 solution.  
 Acriflavine base N.N.R.  
 Proflavine sulfate B.P.  
 Proflavine sulfate (2,8-diaminoacridinium monohydrogen sulfate) N.N.R.  
 Mercuric chloride B.P. As a disinfectant, 1:1,000-2,000 solution. As an antiseptic, 1:6,000.  
 Mercuric cyanide N.N.R.  
 Mercuric oxycyanide B.P.  
 Mercuric iodide B.P.  
 Potassium mercuric iodide N.N.R.  
 Merbromin N.N.R. Usually used as a 2-5 per cent solution.  
 Merthiolate N.N.R.

Nitromersol N.N.R.

Merphenyl borate, merphenyl nitrate and merphenyl picrate  
N.N.R.

Silver nitrate U.S.P.; B.P.

Toughened silver nitrate (lunar caustic) U.S.P.; B.P.

Silver lactate N.N.R.

Silver picrate N.N.R.

Mild silver protein U.S.P.

Strong silver protein B.P.; N.N.R.

Surgical solution of chlorinated soda (Dakin's solution) B.P.

Chloroazodin U.S.P.

Chloroazodin solution U.S.P.

Chloramine-T. N.N.R. Chloramine B.P.

Dichloramine-T. N.N.R.

Hyclorite N.N.R.

Succinchlorimide N.N.R. (for water disinfection).

Halazone N.N.R. (for water disinfection).

Iodine tincture U.S.P. Contains 20 Gm. iodine, 24 Gm.  
sodium iodide in 1000 cc.

Strong solution of iodine B.P.

Weak solution of iodine B.P.

Iodoform B.P.

Hydrogen peroxide solution U.S.P.; B.P. Approximately 3  
per cent solution.

Sodium peroxide N.N.R.

Medicinal zinc peroxide U.S.P. Contains zinc peroxide, zinc  
carbonate and zinc hydroxide.

Potassium permanganate U.S.P.; B.P.

Alcohol U.S.P.; B.P. Approximately 92 per cent ethyl  
alcohol by weight.

Isopropyl alcohol N.N.R.

Phenol U.S.P.; B.P.

Cresol U.S.P.; B.P. A mixture of isomeric cresols obtained  
from coal tar.

Cresatin N.N.R.

Boric acid U.S.P.; B.P.

Boric-acid ointment U.S.P.; B.P. Contains approximately 10 per cent boric acid.  
 Benzoic acid U.S.P.; B.P.  
 Salicylic acid U.S.P.; B.P.  
 Ointment of salicylic acid B.P. Contains approximately 2 per cent salicylic acid  
 Phenol chloride N.N.R.  
 Benzalkonium chloride U.S.P.  
 Nitrofurazone N.N.R.

## BIBLIOGRAPHY

### GENERAL

Garrod, Lawrence P.: Principles and practice of local chemotherapy, Brit. M. Bull. 4: 275, 1946.  
 Hunter, A. C.: The evaluation of antiseptics, J.A.M.A. 121: 25, 1943.  
 McCulloch, E. C.: Disinfection and Sterilization, Philadelphia, Lea, 1945.

### ACRIDINE DERIVATIVES

Albert, A., S. D. Rubbo, R. J. Goldacre, M. E. Davey and J. D. Stone: The influence of chemical constitution on antibacterial activity, Part 11—a general survey of the acridine series, Brit. J. Exper. Path. 26: 160, 1945.  
 Heggie, J. F., G. B. R. Warnock and R. W. Nevin: "Neutral proflavine sulfate" (monosulfate of 2:8-diamino-acridine), its local action infected wounds involving bone, Brit. M. J. 1: 437, 1945.

Martin, G. J.: Acridine antiseptics, Medicine 23: 79, 1944.

### MERCURY AND SILVER COMPOUNDS

Organic mercurial compounds as bactericidal agents (Council report), J.A.M.A. 115: 2083, 1940.  
 Brewer, J. H.: The antibacterial effects of the organic mercurial compounds with special reference to their use as germicides for the sterilization of surgical and dental instruments, J.A.M.A. 112: 2009, 1939.  
 Hill, W. R., and D. M. Pillsbury: Argyria, the Pharmacology of Silver, Baltimore, Williams & Wilkins, 1939.



Young, H.: A new germicide for use in the genito-urinary tract: "mercurochrome-220," J.A.M.A. 73:1483, 1919.

#### PEROXIDES

Freeman, B. S.: The use of zinc peroxide in malignant lesions, J.A.M.A. 115:181, 1940.

#### ALCOHOLS

Archer, G. T. L.: Bactericidal effect of mixtures of ethyl alcohol and water with special reference to sterilization of the skin, and a note on the comparable effects of ether, Brit. M. J. 2:148, 1945.

Hamburger, M., Jr., O. H. Robertson and T. T. Puck: The present status of glycol vapors in air sterilization, Am. J. M. Sc. 209:162, 1945.

#### DETERGENTS

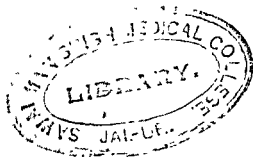
Medical Uses of Soap—A Symposium, Philadelphia, Lippincott, 1945.

Morton, H.: "Germicidal" soap, J.A.M.A. 124:1195, 1944.

#### FURAN DERIVATIVES

Dodd, M. C., and W. B. Stillman: The in vitro bacteriostatic action of some simple furan derivatives, J. Pharmacol. & Exper. Therap. 82:11, 1944.

Downing, J. G., M. C. Hanson and M. Lamb: Use of 5-nitro-2-furaldehyde semicarbazone in dermatology, J.A.M.A. 133:299, 1947.



# Intestinal Anthelmintics

25

INTRODUCTION	
CARBON TETRACHLORIDE AND	THYMOL
TETRACHLOROETHYLENE	BETANAPHTHOL
HEXYLRESORCINOL	METHYLRosaniline
OIL OF CHENOPODIUM	CHLORIDE
SANTONIN	ASPIDUM
MISCELLANEOUS AGENTS	
PREPARATIONS	

## INTRODUCTION

Anthelmintics are drugs used to rid the body of worms. They are sometimes classified as vermifuges, which have a direct lethal action on the worm, and vermicides, causing evacuation of the worms without exerting a direct lethal effect.

Most parasitic worms are found only in the gastro-intestinal tract, notable exceptions being the schistosoma, filaria and trichinella, which are tissue invaders. The prime requisites for an intestinal anthelmintic are low toxicity when applied locally to mucous surfaces and either low toxicity after absorption or the property of nonabsorbability from the gastro-intestinal tract. Many of the drugs discussed in this chapter would, if absorbed, cause serious toxic effects or death with much lower doses than those required for eradication of the parasites. Hence, the mechanism of the chemotherapeutic action of these agents is not a specific differential toxicity towards the host and the parasite but is a matter of localization of the drug on or within the parasite.

In practice, a certain amount of absorption of these drugs from the gastro-intestinal tract invariably occurs. The possibility of toxic effects can be minimized, however, by certain precautionary measures. Thus, the presence of alcohol and of fatty foods in the gastro-intestinal tract may increase the absorption of the anthelmintic to a dangerous degree; therefore, these must be avoided for a day or two before the drug is given. Many of the anthelmintics have a deleterious action on the liver and especially on a glycogen-depleted liver, hence the state of nutrition of the patient may have a marked influence on the toxicity of these drugs. Best results are usually obtained if the patient is allowed a light meal 12 hours before the drug is to be given.

Anthelmintics should always be followed promptly by purgation. This serves the dual function of sweeping out the dead or dying worms and removing the potentially toxic anthelmintic. In general, saline purgatives are recommended. Most anthelmintics are fat-soluble, and oily purges are said to facilitate their absorption, but this is probably only true in the case of absorbable oily purgatives, such as olive oil.

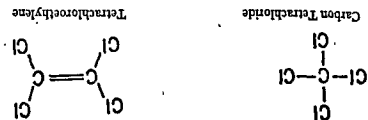
While each anthelmintic exerts some deleterious action on all of the common worms, it is usually particularly effective against one species. Stool examinations should be made, therefore, to identify the particular parasite or parasites present so that the most effective agent may be chosen.

A single administration of an anthelmintic is not always sufficient to eradicate the infestations completely. If successive doses of anthelmintics are required, they should be adequately spaced to avoid cumulative poisoning. The effectiveness of the treatment may be determined by demonstration of egg-free stools after an appropriate period of time. With tapeworms, cures cannot be expected unless the head is removed.

In severe helminth infections, the use of anthelmintics should be supplemented or even in some cases preceded by supportive measures including the use of iron or blood trans-

fusions if anemia exists, the administration of adequate foods and vitamins and the use of antibiotics or sulfonamides if secondary infection exists. It should also be realized that worm eradication must usually be carried out on a family, institutional or community basis since infestations are rarely confined to one individual and reinfection may readily occur. In the case of mass treatment, it is important to use a preparation that can be administered effectively with a minimal amount of supervision and that is relatively nontoxic and comparatively inexpensive.

## CARBON TETRACHLORIDE AND TETRACHLOROETHYLENE

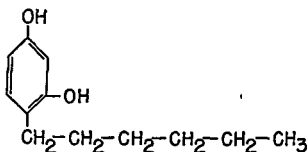


Carbon tetrachloride was introduced in 1921 by Hall, who demonstrated its effectiveness in helminth infestations in dogs and horses and suggested its use in human beings. Its value in the treatment of hookworm disease in human beings was immediately established and because of its efficacy and cheapness it soon became widely used. It soon became apparent, however, that carbon tetrachloride produced severe liver and kidney damage if sufficient amounts were absorbed. Extensive experimental and clinical studies indicated that its toxicity could be greatly reduced if the patient were given a carbohydrate- and calcium-rich diet and were warned to abstain from alcohol and fatty foods. Meanwhile, in 1925, Hall and Shillingher demonstrated that tetrachloroethylene was almost as effective an anthelmintic as carbon tetrachloride and much less toxic. This drug has

now almost entirely replaced carbon tetrachloride as an anthelmintic. As far as is known, no fatalities have followed its use, the occasional toxic reactions being limited to giddiness, nausea and vomiting. Rarely, a soporific effect is produced.

Tetrachloroethylene or carbon tetrachloride apparently narcotize rather than kill the hookworms, hence their administration must be followed promptly by a saline cathartic. These drugs are contraindicated in the presence of ascaris infestations since they cause a primary stimulation of these worms which may lead to the formation of obstructing masses in the intestine or to migration of worms into the biliary or pancreatic duct, stomach or esophagus.

### HEXYLRESORCINOL



Hexylresorcinol

Hexylresorcinol is one of the safest and most widely used anthelmintics. It is used chiefly in the treatment of ascariasis but is also of some value in the eradication of dwarf tapeworms, hookworms and pinworms. It was introduced as an antiseptic in 1927, its anthelmintic properties being first established by Lamson in 1930. It owes its effect to a blistering action on the cuticle of the worm. Its efficacy is greatly reduced by the presence of protein material in the gastro-intestinal tract, hence, *purgation or fasting should precede its use.*

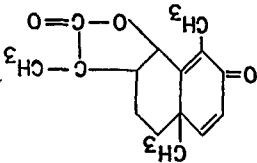
When used as an anthelmintic, hexylresorcinol is administered in crystalline form, usually in capsules or coated pills, since it may cause a burning sensation in the mouth, followed by anesthesia and ulceration of the oral mucous membrane.

### OIL OF CHENOPODIUM

Oil of chenopodium is a volatile oil obtained from American wormseed (*Chenopodium ambrosioides*). It owes its anthelmintic properties to an organic peroxide, ascaridol. It is of greatest value in the treatment of tapeworm and whipworm. It is said to be more effective on the Old World hookworm but less effective on the American species than carbon tetrachloride or tetrachloroethylene.

Oil of chenopodium is quite toxic and commonly gives rise to dizziness, nausea, ringing in the ears and occasionally to deafness. In fatal cases, convulsions and coma occur. Children and debilitated persons are especially susceptible. Its toxicity is due both to a local irritating action on the gastro-intestinal and urinary tracts and to a central depressant action on the respiratory and circulatory centers.

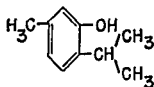
### SANTONIN



Santonin is a crystalline principle obtained from various species of *Artemisia* (Levant wormseed), the anthelmintic properties of which have been recognized for centuries. It is

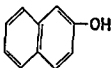
most effective in the treatment of ascariasis; it does not kill the worms but renders them easily removable with a purge. However, it is quite toxic, causing vomiting, colic and diarrhea, hallucinations and convulsions. The urine is sometimes colored yellow or green. Disturbances in color vision are common, especially "yellow vision" (xanthopsia).

### THYMOL



Thymol is a crystalline phenol derivative prepared synthetically or obtained from the volatile oils of a number of different plants. It was first used in the treatment of hookworm infections by Bozzolo in 1879 in Italy. It is little used now because of its toxicity. Symptoms of poisoning include gastro-intestinal upsets, ringing in the ears, dizziness and muscular weakness.

### BETANAPHTHOL



Betanaphthol was introduced for the treatment of hookworm in 1906. It is little used now as an anthelmintic except in the treatment of fasciolopsiasis because of its toxic effects, which include gastro-intestinal upsets and central nervous system stimulation. Hemolysis of red blood cells has also been reported following its use.

Betanaphthol has a marked germicidal effect. Its greatest use is in the treatment of parasitic skin diseases usually in the form of an 0.5 to 5 per cent ointment. It is also used as an intestinal antiseptic.

## METHYLTROSANILINE CHLORIDE

Methylrosaniline chloride (gentian, methyl, crystal violet) is a mixture of hexa-, penta- and tetra-methyl-p-rosaniline chlorides. It was first introduced as an antiseptic but has recently been used effectively as an anthelmintic in strongyloidiasis and oxyuriasis. Untoward effects are usually of a temporary nature and include nausea, vomiting, diarrhea and abdominal pain. It is generally administered in enteric-coated pills, which minimize the gastric irritation caused by this drug.

Methylrosaniline chloride is also used as an anti-infective in pyogenic skin infections, in fungus infections and in burns.

## ASPIDIUM

Aspidium is a crude drug obtained from the European Aspidium (male fern) or American Aspidium (marginal fern). It has been used as an anthelmintic for centuries. It is of particular value in the treatment of teniasis, being probably the most effective agent available against tapeworms. It narcotizes rather than kills the worms, hence must be followed by a purge. It is occasionally absorbed in sufficient quantities to cause severe toxic effects, including dizziness, headache, convulsions, hallucinations, visual disturbances and kidney damage. It is usually administered nowadays as the oleoresin, which is considerably less toxic than the crude drug.

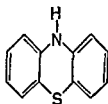
## MISCELLANEOUS AGENTS

Phenothiazine was introduced as a veterinary anthelmintic in 1933. It was first used in the treatment of threadworm and roundworm infections in human beings by Manson-Bahr in 1940. However, subsequent workers were not so enthusiastic concerning its efficiency, while its toxicity, particularly its destructive action on red blood cells,



has led to its virtual abandonment in the treatment of human helminth infestation. In animals, overdosage has led to paralysis.

Leche de higuerón is the crude fresh latex of certain species of fig trees of the South and Central Americas. It is used effectively in those countries as a vermicide, especially in ascariasis and trichuriasis. Its activity is apparently due to the presence of a proteolytic enzyme, ficin, which digests the worm. Preparations of leche de higuerón rapidly lose their effectiveness unless refrigerated. Some potency may



Phenothiazine

be retained, however, if sodium benzoate is added as a preservative. Other proteolytic enzymes which have been suggested as anthelmintics include papain, obtained from the papaya, and bromelain, obtained from pineapple juice. The latter has been shown to be effective against ascaris *in vitro* but not *in vivo*. The use of enzyme preparations as anthelmintics should be avoided in cases in which bowel lesions are known or suspected to exist.

Pelletierine tannate is a mixture of the tannates of several alkaloids obtained from pomegranate, whose use in the treatment of tapeworm is mentioned in the writings of Dioscorides. Pelletierine is little used nowadays because of the frequency with which it produces severe toxic effects, including gastro-intestinal upsets, muscular cramps, dizziness and visual disturbances. Occasional cases of permanent blindness have been reported following its use.

Table 6

## COMMON PARASITIC INTESTINAL HELMINTHS

ORGANISM	DISEASE
<i>Ancylostoma duodenale</i> (Old World hookworm)	Ancylostomiasis
<i>Necator americanus</i> (American hookworm)	Necatoriasis, uncinariasis
<i>Ascaris lumbricoides</i> (Roundworm)	Ascariasis
<i>Enterobius vermicularis</i> (Pinworm, seatworm, oxuris)	Enterobiasis, oxyuriasis
<i>Strongyloides stercoralis</i> (Feltworm)	Strongyloidiasis
<i>Trichuris trichiura</i> (Whipworm)	Trichuriasis

Platyhelminthes  
(Flatworms)

<i>Diphyllobothrium latum</i> (Dwarf tapeworm)	Diphyllobothriasis
<i>Hymenolepis nana</i> (Fish tapeworm)	Hymenolepiasis nana
<i>Tenia saginata</i> (Beef tapeworm)	Teniasis saginata
<i>Tenia solium</i> (Pork tapeworm)	Teniasis solium
<i>Fasciolopsis buski</i> (Large intestinal fluke)	Fasciolopsiasis

## PREPARATIONS

- Tetrachloroethylene U.S.P. 3 cc.  
Tetrachloroethylene capsules. Usually contain 0.2, 1.0 and 2.5 cc.  
Carbon tetrachloride B.P. 2-4 cc.  
Hexylresorcinol U.S.P. 1 Gm.  
Hexylresorcinol pills U.S.P. Usually 0.1 and 0.2 Gm.  
Oil of chenopodium B.P. 0.2-1 cc.  
Santonin B.P. 0.05-0.2 Gm.  
Thymol U.S.P.; B.P. 1-2 Gm.  
Betanaphthol U.S.P.; B.P. 0.12 Gm.  
Methylrosaniline chloride U.S.P. 60 mg.  
Aspidium U.S.P. Male fern B.P. 4-8 Gm.  
Aspidium oleoresin U.S.P. 4 Gm. Extract of male fern B.P. 2-6 cc.  
Pelletierine tannate B.P. 0.12-0.5 Gm.

## BIBLIOGRAPHY

## GENERAL

- Craig, C. F., and E. C. Faust: Clinical Parasitology, Philadelphia, Lea, 1945.  
Einhorn, H. E., and J. F. Miller: Intestinal helminthiasis: clinical survey of six hundred and eighteen cases of infection with common intestinal helminths in children, *Am. J. Trop. Med.* 26:497, 1946.  
Faust, E. C.: The chemotherapy of intestinal parasites, *J.A.M.A.* 117:1331, 1941.

## CARBON TETRACHLORIDE AND TETRACHLOROETHYLENE

- Hall, M. C.: The use of carbon tetrachlorid for the removal of hookworms, *J.A.M.A.* 77:1641, 1921.  
Lamson, P. D., G. H. Gardner, R. K. Gustafson, E. D. Maire, A. J. McLean and H. S. Wells: The pharmacology and toxicology of carbon tetrachloride, *J. Pharmacol. & Exper. Therap.* 22:215, 1923.  
Lamson, P. D., B. H. Robbins and C. B. Ward: The pharmacology and toxicology of tetrachlorethylene, *Am. J. Hyg.* 9:430, 1929.

Most, H., J. M. Hayman and T. B. Wilson: Hookworm infections in troops returning from the Pacific, *Am. J. M. Sc.* 212: 347, 1946.  
 Sandground, J. H.: Coma following medication with tetrachlorethylene, *J.A.M.A.* 117: 440, 1941.

# HEXYLRESORCINOL

Einhorn, N. H., J. F. Miller and L. Whittier: Ascariasis clinical survey of one hundred and twenty-five cases of infection with *Ascaris lumbricoides* in children, *Am. J. Dis. Child.* 69: 237, 1945.  
 Lamson, P. D., E. L. Caldwell, H. W. Brown and C. B. Ward: Hexylresorcinol in the treatment of human ascariasis, *Am. J. Hyg.* 13: 568, 1931.  
 Trim, A. R.: Experiments on the mode of action of hexyl resorcinol as an anthelmintic, *Parasitology* 35: 209, 1943-1944.

# OIL OF CHENOPODIUM

Smilie, W. G., and S. B. Pessoa: A study of the anthelmintic properties of the constituents of the oil of chenopodium, *J. Pharmacol. & Exper. Therap.* 24: 359, 1925.

# METHYLROSANILINE CHLORIDE

Evans, H. L., and H. Moore: A comparison of gentian violet and hexylresorcinol in the treatment of pinworm infestation, *J. Pediat.* 20: 627, 1942.  
 Wright, W. H., and F. J. Brady: Studies on oxyuriasis XXII—the efficacy of gentian violet in the treatment of pinworm infestation, *J.A.M.A.* 114: 861, 1940.

# MISCELLANEOUS PREPARATIONS

Bercovitz, Z., R. C. Page and E. J. de Beer: Phenothiazine—experimental and clinical study of toxicity and anthelmintic value, *J.A.M.A.* 122: 1006, 1943.  
 Faust, E. C., and L. F. Thomen: Parasitological properties of the proteolytic enzyme ficin, *Proc. Soc. Exper. Biol. & Med.* 47: 485, 1941.  
 Molitor, H., C. W. Mushett and S. Kuna: Some toxicological and pharmacological properties of the proteolytic enzyme, ficin, *J. Pharmacol. & Exper. Therap.* 71: 20, 1941.

# Amebacides

INTRODUCTION

IODOQUINOLINE DERIVATIVES

EMETINE

ARSENICALS

PREPARATIONS

## INTRODUCTION

Amebacides are drugs lethal to amebae. They are used principally in the treatment of infections of *Entameba histolytica*, amebiasis. The choice of drugs and the success of the treatment are governed largely by the location of the parasites, the duration of the disease, the presence or absence of secondary bacterial infections and the general health of the patient.

In its mildest form, amebiasis consists of the presence of *Entameba histolytica* in the lumen of the large intestine with or without some penetration or ulceration of the mucosa. It has been estimated that from 10 to 20 per cent of the population of the United States harbor the parasite in this form and act as symptom-free carriers of the disease. If the bowel involvement is more severe, symptoms of dysentery or chronic diarrhea develop, the so-called amebic dysentery or amebic colitis. If untreated, this stage may progress to amebic hepatitis or the more severe amebic abscess through secondary invasion of the liver. More rarely, there may be invasion of the lung or the brain.

The vegetative form of the parasite responsible for the pathogenicity of the disease does not survive long outside the body and is destroyed by gastric acidity. The encysted form is quite resistant in moist surroundings and is responsible for the transmission of the disease. It may be destroyed

by heat, drying, chlorine, iodine or detergents, or may be removed by filtration.

Three types of compounds are the main therapeutic agents used in the treatment of amebiasis: emetine, iodoquinoline derivatives and arsenicals. None of these agents is effective against all stages of the disease, so that a course of treatment consists of the alternate use of two or more preparations. This has the further advantage of reducing the possibility of drug-fastness, which may develop with the prolonged or repeated use of a single drug. Amebic abscesses usually require surgical drainage and if secondarily infected, one of the sulfonamides or antibiotics should be used. The general health of the patient should be sustained by an adequate diet with vitamin supplements when necessary. The anemia which is frequently present in long-standing infections responds well to liver extract and iron. Unless treated early, amebiasis may prove very difficult to cure. Chronic cases of amebic dysentery may be complicated by coexisting bacterial infections; in some of these cases, dramatic improvement has followed the use of penicillin and the sulfonamides.

It should not be forgotten that chronic sufferers of amebiasis tend to get discouraged by long series of unsuccessful therapy. Every effort should be made towards reassuring them, and towards providing suitable occupational therapy while treatment is in progress.

## EMETINE

Emetine is an alkaloid obtained from *ipecacuanha*, the dried root of *Cephaelis ipecacuanha* or *acuminata*. *Ipecacuanha* or *ipecac* was brought to Europe from Brazil in 1658 for the treatment of dysentery. Since it was not until 1905 that it was shown to be effective only in amebic and not in bacillary dysentery, it is not surprising that during the intervening centuries it was greeted with alternate enthusiasm and disappointment.

# Amebacides

INTRODUCTION

IDOQUINOLINE DERIVATIVES

EMETINE

ARSENICALS

PREPARATIONS

## INTRODUCTION

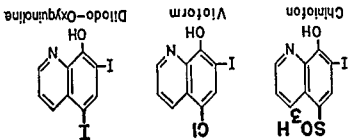
Amebacides are drugs lethal to amebae. They are used principally in the treatment of infections of *Entameba histolytica*, amebiasis. The choice of drugs and the success of the treatment are governed largely by the location of the parasites, the duration of the disease, the presence or absence of secondary bacterial infections and the general health of the patient.

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administration of opium or of tannic-acid preparations. Bismuth subnitrate or subcarbonate, either alone or in combination with emetine, has had some use in the treatment of intestinal amebiasis, but it is probably because they act largely as protectives and demulcents on the inflamed mucous membrane of the colon.

## IDOQUINOLINE DERIVATIVES



The iodoquinoline derivatives are the safest and most efficient agents available for the treatment of intestinal amebiasis. They are of no value, however, in the treatment of amebic hepatitis or amebic abscess. Their efficacy is due to liberated iodine, which has a lethal effect on both encysted and vegetative forms. In therapeutic doses, toxic effects are rare, though many patients experience a profuse diarrhea, especially during the first few days of treatment. Occasionally, sufficient iodine may be absorbed to give symptoms of iodism, of which skin eruptions and salivation are the most common manifestations. Liver damage has been demonstrated experimentally and the iodoquinoline derivatives should be avoided in cases of hepatic impairment. Chiniofon (yatren) was introduced as an amebicide in 1921. It is marketed as a mixture of chiniofon, its sodium salt and sodium bicarbonate. It can be administered orally in tablet form or rectally as a retention enema. It has been advocated as a prophylactic agent for individuals required to spend short periods of time in regions in which amebiasis is endemic.



In 1817, Pelletier obtained an active alkaloidal fraction from crude ipecac. This was later shown to consist of at least four alkaloids, of which emetine is the most important. Emetine did not replace ipecac in the treatment of amebiasis for many years after its isolation, largely because of the mistaken notion that it represented the emetic but not the parasitical activity of the crude drug. In 1911, however, Vedder demonstrated the amebacidal action of emetine by *in vitro* studies, and the following year Rogers reported the successful treatment of amebic dysentery and hepatitis with intramuscular injections of soluble emetine salts.

Emetine is a toxic drug and should be administered only under hospital supervision. It produces depression, muscular weakness, nausea and diarrhea. It has a direct toxic action on the heart which may result in cardiac irregularities and a fall in blood pressure. Its dangers are minimized, however, if the patient is kept in bed during treatment and if the therapeutic dose is not exceeded. Emetine is only slowly excreted from the body, which results in accumulation of the drug in the body during the course of treatment, with the attendant possibility of late toxic effects.

Emetine is the only effective amebicide for the treatment of amebic hepatitis or amebic abscess. It is of little value in the treatment of intestinal amebiasis, however, for while it may temporarily relieve the symptoms it only rarely completely eradicates the parasites. It is without effect on encysted stages of the parasites.

A number of insoluble emetine preparations have been introduced which can be taken orally. These drugs offer little, however, since they are more erratic in action than parenteral emetine and cause more gastro-intestinal disturbances. Emetine and bismuth iodide (E.B.I.) is probably the most widely used of such preparations and may owe some of its effectiveness to its iodine content. Ipecac is still used to some extent because of its availability and lower cost. Gastro-intestinal upsets from its use may be reduced by the

## PREPARATIONS

Ipecacuanha U.S.P.; B.P. 0.5 Gm.  
 Emetine hydrochloride U.S.P.; B.P. 60 mg.  
 Emetine-hydrochloride injection U.S.P. Usually available  
 in ampuls containing the following amounts of emetine  
 hydrochloride: 20 mg. in 1 cc.; 30 mg. in 1 cc.; 60 mg.  
 in 1 cc.

Emetine and bismuth iodide B.P. 0.06-0.2 Gm.

Chiniofon U.S.P.; B.P. 0.5-1.0 Gm.

Chiniofon tablets U.S.P. Contain 0.25 Gm. chiniofon.

Iodochloroxyhydroxyquinoline N.F. 0.5 Gm.

Diiodo-oxyquinoline N.N.R. 0.5 Gm.

Carbarsone U.S.P. 0.25 Gm.

Acetarsone N.N.R. Acetarsol B.P. 0.25 Gm.

## BIBLIOGRAPHY

## GENERAL

Adams, A. R. D.: Amoebiasis with special reference to  
 treatment, Tr. Roy. Soc. Trop. Med. & Hyg. 38: 237,  
 1945.  
 Albright, E. C., and E. S. Gordon: Present status of the  
 problem of amoebiasis, Arch. Int. Med. 79: 253, 1947.  
 Amoebiasis: War Dept. Tech. Bull. 159, War Med. 7: 390,  
 1945.

Craig, C. F.: The Etiology, Diagnosis and Treatment of  
 Amoebiasis, Baltimore, Williams & Wilkins, 1944.

Harcreaves, W. H.: Chronic amoebic dysentery—new  
 approach to treatment, Lancet 2: 68, 1945.

Noth, P. H., and J. W. Hirschfeld: Amoebic abscess of the  
 liver with secondary infection: local treatment with

penicillin, J.A.M.A. 124: 643, 1944.

Ochsner, A., and M. DeBakey: Amoebic hepatitis and  
 hepatic abscess, Surgery 13: 460 (March), 612 (April),  
 1943.

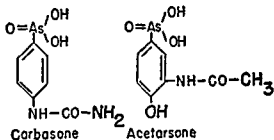
## EMETINE

Hardgrove, M., and E. R. Smith: Effects of emetine on  
 the electrocardiogram, Am. Heart J. 28: 752, 1944.

Iodochlorohydroxyquinoline (vioform), like chiniofon, was first introduced as an iodoform substitute for wound antisepsis. It is more irritating to mucous surfaces than chiniofon and cannot be given rectally. It is more likely to cause nausea, vomiting and diarrhea.

Diiodo-oxyquinoline (diodoquin) is the most recently introduced of this series, having been overlooked for many years because of its extreme insolubility. Animal experiments indicate that it is poorly absorbed and relatively non-toxic. However, absorption does occasionally occur in both animals and man and toxic symptoms characteristic of iodine poisoning have recently been described following therapeutic doses. Blood levels of iodine may increase ten or a hundred-fold during its use.

### ARSENICALS



The organic arsenicals, like the iodoquinolines, are only effective in treating intestinal amebiasis. Their activity is due to their arsenic content. They may give rise to symptoms of arsenic poisoning, including liver and kidney damage, fever, diarrhea and skin eruptions. They should not be used in the presence of liver or kidney disease.

Carbarsone, introduced as an amebicide in 1932, is probably the safest of these preparations. It is given by mouth or as a retention enema. *Acetarzone* (stovarsol) was introduced as an amebicide in 1923. It is seldom employed now because of its toxicity.

# Antisypilitic Drugs

27

INTRODUCTION  
ARSPHENAMINES  
MISCELLANEOUS AGENTS  
PREPARATIONS  
ARSENOXIDES

The drugs discussed in this chapter are used principally for the treatment of syphilis. They are also effective in other spirochetal infections, such as yaws, relapsing fever and Vincent's angina, while some of the arsenic preparations are used in other parasitic infections, notably trypanosomiasis and, to a lesser extent, amebic dysentery and malaria. The clinical evaluation of a new antisypilitic drug involves many factors, some of which, such as the incidence of late relapse following treatment, may require years of observation of large numbers of patients. For example, while preliminary studies indicate that penicillin shows considerable promise of becoming one of the most useful drugs in this field, several years must elapse before its true role in the treatment of syphilis can be established. Syphilis was first described in the fifteenth century but successful treatment was not available until the introduction of arsphenamine ("salvarsan") by Ehrlich in 1909. Previously, mercury and the iodides had long been used but these drugs merely aided in the healing of open syphilitic lesions without exerting any curative action. The research work culminating in the discovery of arsphenamine laid the foundation for modern chemotherapy. Ehrlich's work was stimulated by the earlier studies of Heubel on the fixation of lead by certain tissues of the

Rogers, L.: The rapid cure of amoebic dysentery and hepatitis by hypodermic injection of soluble salts of emetine, Brit. M. J. 1: 1424, 1912.

#### IDOQUINOLINES

David, N. A. V., N. M. Phatak and F. B. Zener: Iodo-chlorhydroxyquinoline and diiodohydroxyquinoline; animal toxicity and absorption in man, Am. J. Trop. Med. 24: 29, 1944.

Hummel, H. G.: A critical appraisal of the newer amebicides and the results of treatment of amebiasis with di-iodohydroxyquinoline (diodoquin), Am. J. Digest. Dis. 6: 27, 1939.

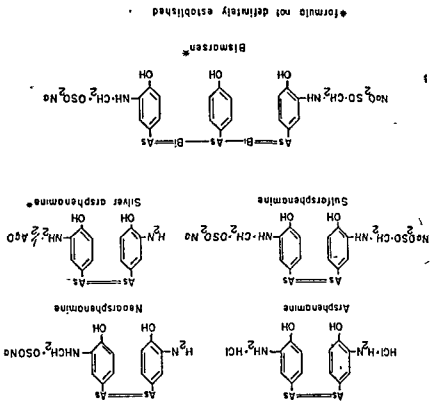
Silverman, D. N., and A. Leslie: Toxic effects of diodoquin, J.A.M.A. 128: 1080, 1945.

#### ARSENICALS

Epstein, E.: Toxicity of carbarsone, J.A.M.A. 106: 769, 1936.

Reed, A. C., H. H. Anderson, N. A. David and C. D. Leake: Carbarsone in the treatment of amebiasis, J.A.M.A. 98: 189, 1932.

Arsphenamine is a semicrystalloid preparation marketed as the soluble dihydrochloride salt. Before injection, solutions of the drug must be made alkaline, since injection of acid solution results in intravascular precipitation of the drug. The alkalinized solution, consisting of a mixture of



the mono- and disodium salts, must be injected intravenously because of its irritating properties. Following the injection of arspenamine, arsenic appears in the urine within a few hours. The maximal excretion occurs from 24 to 48 hours after administration, but arsenic can be demonstrated in the urine for many days. A large fraction of the dose is excreted in the bile and appears in the feces.

body and by his own observations on the differential staining capacity of various dyes. From these experiments he conceived the idea of developing drugs which are specifically attracted to the pathogenic organism rather than to the tissues of the host in the hope of exerting a toxic effect on the invading organisms without affecting adversely the tissues of the host. Ehrlich applied the term "chemoreceptors" to those hypothetical groups in the parasite responsible for fixation of the drug and expressed the relative toxicity of the drug to the parasite and to the host as the "chemotherapeutic index." This term is still retained to express the ratio of the minimum effective dose to the maximal tolerated dose.

It should be pointed out that Ehrlich's work in developing new antisymphilitic agents was greatly aided by three contemporary advances in the field of syphilology, namely, the transmission of syphilis to experimental animals by Metschnikoff and Roux in 1903, the discovery of the causative agent, *Treponema pallidum* by Schaudinn in 1905 and the development by Wassermann in 1907 of a blood test for syphilis. Finally, the recognition by Hata, the Japanese chemist who collaborated with Ehrlich, of the incorrectness of the accepted structural formula for atoxyl, an organic arsenical introduced in 1904 for the treatment of trypanosomiasis and relapsing fever, led to the determination of its real nature and to the synthesis of related compounds, culminating in the development of the arspenamines.

### ARSPHENAMINES

Arsphenamine (salvarsan, 606, old arspenamine) was the six hundred and sixth of a series of compounds prepared by Ehrlich and his associates. After its spirocheticidal action was demonstrated, Ehrlich named it salvarsan, "saviour of mankind." When manufacture was commenced in the United States during World War I, the drug was officially designated as arspenamine.

**Mode of Action of the Arsphehnamines.** It is generally believed that the arsphehnamines themselves do not possess any spirocheticidal action but that their activity is due to their oxidation products, the arsenoxides, which are fixed by the tissues of the body and by the parasites. The degree of fixation is dependent on the organic part of the molecule, some compounds being adsorbed more readily than others. This portion of the molecule is also responsible for the differential absorption by the spirochetes, thus accounting for the variations among the chemotherapeutic indices of these compounds.

The lethal effect of the arsenoxides is believed to be due to their reaction with sulphydryl compounds of the cell in which they become adsorbed. This is supported by the chemical reactivity between arsenoxides and compounds possessing free sulphydryl groups and by the antidotal action of sulphydryl compounds, such as cysteine, glutathione and dithioglycerol ("BAL") against toxic doses of arsphehnamines and arsenoxides.

**Toxicity of the Arsphehnamines.** General reactions to arsphehnamines include the nitritoid crisis and the Jarisch-Herxheimer reaction, skin lesions, blood dyscrasias, central nervous system disturbances, gastro-intestinal upsets and renal injuries. Local irritation and necrosis may occur from intramuscular injection of irritating preparations while sudden collapse and death usually follow the accidental injection of unneutralized arsphehnamine.

The nitritoid crisis is characterized by the sudden onset of flushing of the face, edema of the tongue and lips, nausea and vomiting, profuse perspiration, fall in blood pressure and a feeling of anxiety. This syndrome is referred to as the nitritoid crisis because of the similarity of the effects to those produced by the administration of nitrites. They are probably due to the formation of minute pulmonary emboli since they rarely occur from the use of crystalloid arsenicals such as oxophenarsine and may be minimized by slow ad-



The treatment of syphilis with the arsphenamines usually requires weekly injections for a period of from 6 months to 2 years. Many patients fail to complete such a schedule. Consequently, the intensive treatment methods, using the arsenoxides or penicillin, are proving increasingly more popular. The arsphenamines are too slowly detoxified by the body to be used in these procedures.

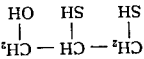
Neoarsphenamine (neosalvarsan, 914) was also developed by Ehrlich. It differs from arsphenamine in that it can be used immediately after solution in water. However, solutions oxidize even more rapidly than those of arsphenamine, hence they should be injected within 20 minutes. Neoarsphenamine is always injected intravenously. It is somewhat less active than arsphenamine and somewhat higher doses and a more prolonged period of treatment are usually necessary.

Sulfarsphenamine was introduced into the United States in 1922 by Voegtlin and Johnson. It is acid in reaction, about as active as neoarsphenamine, and is extremely resistant to oxidation by air. It can be injected intramuscularly, which is of particular value in the treatment of children.

Silver arsphenamine was developed in Germany by Kolle. It is of the same order of activity as neoarsphenamine. It is less likely to produce toxic reactions but argyria may result from its long-continued use. It need not be alkalized before use but solutions must be injected within 20 minutes since they deteriorate both by oxidation and by precipitation of the silver by the carbon dioxide in the air.

Bismarsen (bismuth arsphenamine sulfonate) is a water-soluble organic preparation containing approximately 13 per cent arsenic and 24 per cent bismuth. It was prepared by Raiziss in 1927. It must be administered intramuscularly since it is very toxic when given intravenously. It is a relatively weak and slow-acting drug but is of value when intravenous medication is impossible or contraindicated.

"BAL" in the Treatment of Arsenic Poisoning. "BAL" (British Anti-Lewisite, dithioglycerol, 2-3 dimercaptopropanol) was introduced by British scientists during World War II as an antidote for the arsenic-containing chemical warfare agent, Lewisite. It has recently been used in the



treatment of arsenic and mercury poisoning and in antidoting the toxic effects of therapeutic arsenicals, antimonials, mercurials and gold compounds. Since its action is to remove the drug from the living cell, it also reduces the therapeutic effects of these preparations. Overdosage with "BAL" leads to acidosis and hyperglycemia, increased depth and rate of respiration, tremors, tachycardia and, finally, tonic and clonic convulsions. The drug is marketed in a benzyl benzoate—peanut-oil solution for intramuscular injection and in combination with glucose as BAL-glucoside for intravenous medication. Control of Arsphenamines and Arsenoxides. The distribution of trivalent arsenicals in the United States is supervised by the United States Public Health Service. Manufacture may be carried out in licensed laboratories only and the arsenic content and toxicity in animals of each drug lot must be determined. Essentially similar regulations are in force in Great Britain.

### ARSENOXIDES

Oxophenarsine (mapharsen, mapharside "arsenoxide") is the arsenoxide of arsphehnamine and presumably the active metabolite of the latter drug. It was tested as an antisyphilitic agent by Ehrlich but he considered that its toxicity precluded its clinical use. In 1932, however, Tatum and Cooper restudied the drug and recommended its clinical trial.

ministration of the drug. Severe cases may be followed by complete collapse and death. Epinephrine is a great help in combatting this reaction and may on occasion be life-saving.

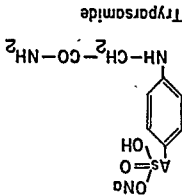
The Jarisch-Herxheimer reaction may appear from 2 to 3 hours after the injection is completed. It consists of an intensification of secondary eruptions and, in late syphilis, may occasionally result in death by coronary occlusion, by asphyxia in cases of gumma of the larynx or by cerebral hemorrhage. The reaction may be avoided by preliminary treatment with small doses of arsphenamines or by preparatory treatment with bismuth or mercury preparations and potassium iodide.

The arsphenamines can produce almost any form of dermatitis, due in part to overdosage and in part to sensitization. Desensitization in these cases is not successful and should never be attempted since minute amounts of any of the organic arsenicals can cause a recurrence. The most severe reaction is exfoliative dermatitis. Another reaction is known as "erythema of the ninth day." It occurs within the first 2 weeks after the first injection of arsphenamine and is characterized by erythema, malaise and a rise in temperature.

Blood changes are severe though relatively infrequent complications during the administration of arsenicals. They are due to depression of the bone marrow and include aplastic anemia, granulocytopenia and thrombocytopenia. Jaundice may occur during the course of treatment. In some cases, this has been proved to be due to infectious hepatitis, transmitted by improperly sterilized syringes. Toxic encephalopathy is a rare but serious complication of arsenic therapy. Gastro-intestinal upsets are frequent and many patients complain of a garlic or ether odor following injection of arsphenamine and neoarsphenamine. It can be avoided if the patient holds his nose and breathes through his mouth.

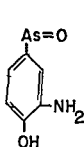
hours. The incidence of untoward reactions is very high, however, and the therapeutic results are poor. Dichlorophenarsine (chlorarsen, phenarsine) was introduced for the treatment of syphilis in 1941. It is rapidly broken down in the body to oxophenarsine. It offers the advantage of greater stability in storage; its use and effectiveness are otherwise identical to that of oxophenarsine.

## MISCELLANEOUS AGENTS

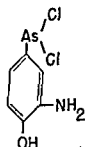


Tryparsamide is a pentavalent arsenical originally introduced by Jacobs and Heidelberger of the Rockefeller Institute in 1919 for the treatment of trypanosomiasis. Its spirocheticidal action is weak and it is used only in syphilis of the central nervous system. Its use is based on the belief that it, in contrast to most of the trivalent arsenicals, readily penetrates the meninges. Tryparsamide, in common with many pentavalent arsenicals, has a tendency to produce visual disturbances because of a specific toxic effect on the optic nerve. Gastro-intestinal disturbances and nitritoid reactions occur, as with other arsenicals. The relatively low potency of the drug explains the low incidence of Herxheimer reactions. Tryparsamide remains the drug of choice in the treatment of late trypanosomiasis.

Oxophenarsine is a pure chemical compound available in crystalline form. It is relatively unstable even in the dry state, decomposition being accompanied by a brownish discoloration and an increase in the toxicity. It does not require alkalization. It must be given intravenously. It is ten times more active than arsphenamine but less toxic in therapeutic doses. It is detoxified more rapidly than arsphenamine and is sometimes administered at more frequent intervals.



Oxophenarsine



Dichlorophenarsine

The toxic reactions following the use of oxophenarsine are, in general, similar to, though less frequent than, those following the arsphenamines. The Herxheimer reaction is likely to occur more frequently and be more serious than with the arsphenamines but the nitritoid reaction is seldom seen. Pain in the arm frequently occurs, due to spasm of the injected vein.

The greater effectiveness of oxophenarsine and the rapidity of its action have led to the almost exclusive use of this compound in the intensive arsenotherapy of syphilis. This mode of treatment consists of continuous intravenous administration or repeated injections at frequent intervals over periods varying from 5 to 20 days. The shorter periods of treatment are accompanied by a higher incidence of untoward reactions. The so-called "1-day treatment" consists of intensive chemotherapy and fever therapy over 24

**Fever Therapy.** The apparent intolerance of spirochetes to high temperatures has led to the use of fever therapy in the treatment of syphilis, especially in neurosyphilis. Ideally, a temperature of 106° F. should be reached and maintained over a period of time, during which antisyphilitic drugs may be administered. Fever may be produced by malaria, by the injection of foreign proteins and vaccines or by physical means. While fever therapy is of established value, the medical supervision and nursing care required tend to limit its use. Furthermore, it is contraindicated in the presence of diseases of the cardiovascular and respiratory systems.

## PREPARATIONS

- Arsphenamine U.S.P. 0.3 Gm. intravenous.  
 Neosarsphenamine U.S.P.; B.P. 0.45 Gm. intravenous.  
 Sulfarsphenamine U.S.P.; B.P. 0.45 Gm. intramuscular.  
 Silver arsphenamine N.N.R. 0.2 Gm. intramuscular.  
 Bismarsen N.N.R. 0.2 Gm. intramuscular.  
 Oxophenarsine hydrochloride U.S.P. 0.045 Gm. intravenous.  
 Dichlorophenarsine hydrochloride U.S.P. 0.045 Gm. intravenous.  
 Tryparsamide U.S.P.; B.P. 2 Gm. intravenous.  
 Sodium iodide U.S.P.; B.P. 0.3 Gm.  
 Potassium iodide U.S.P.; B.P. 0.3 Gm.  
 Bismuth potassium-tartrate U.S.P. 0.1 Gm. intramuscular.  
 Bismuth-potassium-tartrate injection U.S.P. Water solution or oil suspension. 0.1 Gm. intramuscular.  
 Bismuth subsalicylate U.S.P.  
 Bismuth-subsalicylate injection U.S.P. Usually 100 mg. or 120 mg. in 1 cc.  
 Bismuth sodium tartrate B.P.; N.N.R.  
 Bismo-cymol N.N.R.  
 Bismuth ethylcamphorate N.N.R.  
 Iodobismutol with benzocaine N.N.R.  
 Quinine bismuth iodide N.N.R.

**Bismuth.** Bismuth preparations were introduced for the treatment of syphilis in 1921 by Sazerac and Levaditi. They are relatively weak *spirochetocides* and are usually used alternately with the arsenicals to prevent cumulative poisoning by the latter.

A great number of bismuth preparations are on the market. These differ pharmacologically only in respects attributable to the different rates of absorption of the element from the site of injection. The usual dosage is equivalent to 100 mg. of bismuth per week.

Toxic effects with bismuth compounds are rare and seldom call for discontinuance of the drug. Stomatitis, diarrhea, albuminuria and dermatitis may occur. Usually after six or more injections of bismuth, a blue line appears on the gums and may extend to the buccal mucosa. While this may be cosmetically undesirable, it is of no serious significance and does not justify discontinuation of treatment. All bismuth preparations are much more toxic intravenously than intramuscularly. Furthermore, accidental intravenous injections of the oily preparations present the danger of formation of pulmonary emboli. If an artery is penetrated, a local arterial embolus may develop. Oral bismuth preparations include sobisminol and bistrimate.

Mercury has been used in the treatment of syphilis since 1495, but its toxicity is high. Before the introduction of the less toxic bismuth preparations, mercury preparations were used in conjunction with arsenicals. Now, however, they are only used topically for prevention of infection, calomel ointment being the most efficient prophylactic agent available.

Sodium or potassium iodide are useful adjuncts in the treatment of late syphilis. The iodides seem to promote resolution of the gummatous lesions, thus exposing the spirochetes to the action of other drugs or to the natural defense mechanisms of the body. The use of iodides is, however, still empirical.

**Fever Therapy.** The apparent intolerance of spirochetes to high temperatures has led to the use of fever therapy in the treatment of syphilis, especially in neurosyphilis. Ideally, a temperature of 106° C. should be reached and maintained over a period of time, during which antisyphilitic drugs may be administered. Fever may be produced by malaria, by the injection of foreign proteins and vaccines or by physical means. While fever therapy is of established value, the medical supervision and nursing care required tend to limit its use. Furthermore, it is contraindicated in the presence of diseases of the cardiovascular and respiratory systems.

## PREPARATIONS

Arspenamine U.S.P. 0.3 Gm. intravenous.  
 Nearsphenamine U.S.P.; B.P. 0.45 Gm. intravenous.  
 Sulfarsphenamine U.S.P.; B.P. 0.45 Gm. intramuscular.  
 Silver arspenamine N.N.R. 0.2 Gm. intramuscular.  
 Bismarsen N.N.R. 0.2 Gm. intramuscular.  
 Oxophenarsine hydrochloride U.S.P. 0.045 Gm. intravenous.  
 Dichlorophenarsine hydrochloride U.S.P. 0.045 Gm. intravenous.  
 Tryparsamide U.S.P.; B.P. 2 Gm. intravenous.  
 Sodium iodide U.S.P.; B.P. 0.3 Gm.  
 Potassium iodide U.S.P.; B.P. 0.3 Gm.  
 Bismuth potassium tartrate U.S.P. 0.1 Gm. intramuscular.  
 Bismuth-potassium-tartrate injection U.S.P. Water solution or oil suspension. 0.1 Gm. intramuscular.  
 Bismuth subsalicylate U.S.P.  
 Bismuth-subsalicylate injection U.S.P. Usually 100 mg. or 120 mg. in 1 cc.  
 Bismuth sodium tartrate B.P.; N.N.R.  
 Bismo-cymol N.N.R.  
 Bismuth ethylcamphorate N.N.R.  
 Iodobismutol with benzocaine N.N.R.  
 Quinine bismuth iodide N.N.R.



Sobisminol mass N.N.R.  
Iodobismuthite sodium N.N.R.  
Sodium potassium bismuthyl tartrate N.N.R.  
Thio-bismol N.N.R. (sodium bismuth thioglycollate)  
Mercuric salicylate N.N.R.  
Mercury benzoate N.N.R.  
Mercuric oxycyanide N.N.R.  
Mercuric succinimide N.N.R.  
Solution colloidal mercury sulfide N.N.R.

## BIBLIOGRAPHY

### GENERAL

- Ehrlich, P., and S. Hata: *The Experimental Chemotherapy of Spirillooses*, London, Rebman Ltd., 1911.  
Moore, J. E.: *The Modern Treatment of Syphilis*, Springfield Ill., Thomas, 1943.  
Reynolds, F. W., and J. E. Moore: *Syphilis—a review of the recent literature*, Arch. Int. Med. 78: 592, 733, 1945-1946.

### ARSPHENAMINES

- Cannon, A. B., J. K. Fisher, J. J. Rodriguez, G. F. Beattie and E. H. Maechling: Blood and urine arsenic levels of patients with early syphilis under intensive arsenotherapy, Am. J. Syph., Gonorr. & Ven. Dis. 30: 144, 1946.  
Eagle, H., and H. J. Magnuson: The systemic treatment of 227 cases of arsenic poisoning (encephalitis, dermatitis, blood dyscrasias, jaundice, fever) with 2,3-dimercaptopropanol (BAL), Am. J. Syph., Gonorr. & Ven. Dis. 30: 420, 1946.  
Probey, T. F., E. W. Norris, A. V. Diebert and E. V. Price: Sulfarsphenamine in the therapy of syphilis—a comparative study of the toxic manifestations of neoarsphenamine and sulfarsphenamine, Pub. Health Rep. 59: 733, 1944.  
Beeriman, H., and J. H. Stokes: The trivalent arsenicals in syphilis, Part II, treatment reactions, Am. J. M. Sc. 202: 606, 1941.

Voegtlin, C.: The pharmacology of arsphenamine (sarsan) and related arsenicals, *Physiol. Rev.* 5:63, 1925.

#### ARSENOXIDES

Beerman, H., and V.-S. Warmock: Dichlorophenarsine hydrochloride in the treatment of syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* 31:150, 1947.  
Tatum, A. L., and G. A. Cooper: An experimental study of mapharsen (meta-amino parahydroxy phenyl arsine oxide) as an antisyphilitic agent, *J. Pharmacol. & Exper. Therap.* 50:198, 1934.

#### MISCELLANEOUS

Beerman, H., and B. Shaffer: Reactions to tryparsamide—a review of ten years' experience, *Brit. J. Ven. Dis.* 16:145, 1940.  
Eagle, H.: The relative toxicity and therapeutic activity in experimental syphilis of bismuth subsalicylate, bismosol and biliposol, *Am. J. Syph., Gonorr. & Ven. Dis.* 30:549, 1946.  
Fleming, W. L., and M. H. Wolf: The relative prophylactic effectiveness against syphilis of ointments containing calomel in different particle size, *Am. J. Syph., Gonorr. & Ven. Dis.* 30:47, 1946.  
Kendell, H. W.: Fever-chemotherapy, *Clinics* 4:1614, 1946.  
Kolmer, J. A., H. Brown and A. M. Rule: Studies in the bismuth therapy of syphilis, I, A comparative study of the toxicity and therapeutic activity of bismuth compounds commonly employed in the treatment of syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* 23:7, 1939.  
Worms, W.: Prophylaxis of syphilis by locally applied chemicals—methods of examination, results, and suggestions for further experimental research, *Brit. J. Ven. Dis.* 16:186, 1940.

# Antimalarial Drugs

INTRODUCTION

QUININE

QUINACRINE

CHLOROQUINE

PALUDRINE

PAMAQUINE

PENTAQUINE

PREPARATIONS

## INTRODUCTION

The chemotherapy of malaria dates back to the seventeenth century when Jesuit missionaries observed that the Peruvian Indians treated fevers with decoctions of cinchona bark. Until 1926 extracts of cinchona bark or its alkaloïds remained the only specific means of treating malaria despite the attempts of German chemists during World War I to produce a synthetic substitute. Subsequently, however, they introduced both pamaquine and the more useful quinacrine in 1926 and 1932, respectively. No further advances were made in the field until World War II, when the loss of quinine supplies from the Dutch East Indies and the alleged toxicity of quinacrine led to a vast program of experimental and clinical research on antimalarials by American and British scientists which advanced our understanding of the treatment and prevention of malaria and culminated in introduction of three new drugs: chloroquine, paludrine and pentaquine.

The three most important species of plasmodia capable of infecting human beings are *P. falciparum*, *P. vivax* and *P. malariae*, the causative agents of malignant tertian, benign tertian and quartan malaria, respectively. The first

of these, *P. falciparum*, is the most virulent and is also the most responsive to chemotherapy. Infections of *P. ma-*

*lariae* are relatively infrequent.

*Vivax* malaria is a debilitating disease characterized by chronicity and by a low mortality rate. With the possible exception of pamaquine and its homologues, no drug treatment is completely effective for prophylaxis or for cure, although a suppression of the clinical signs and symptoms of the disease may be obtained with one of several drugs of relatively low toxicity. This suppressive action can be put to use to achieve a type of prophylactic effect; although an individual may become infected, all signs and symptoms of the disease can be suppressed until the drug is withdrawn. In the interval, the subject is unaware of having contracted malaria and, in addition, immune processes may advance to the point of being able to cope with the infection after discontinuance of the drug.

There are several possible explanations for the lack of a curative action by quinine, quinacrine, chloroquine and paludrine in vivax malaria. It may be due to a quantitative effect, in that the drugs are simply not sufficiently potent to kill 100 per cent of the organisms. Again, the uneven distribution of these drugs in the body may afford protection against the action of the drug on the parasites in those parts of the body in which the concentration of the drug is low. However, experiments with the intentional inoculation of malaria for therapeutic purposes in patients with syphilis of the central nervous system have shown both of these explanations to be unlikely. Infections induced by the inoculation of blood from an infected donor, in contradistinction to those induced by sporozoite inoculation, are readily cured by any of the so-called "suppressive drugs." Hence, the pre-erythrocytic forms of the parasite, developing in a naturally acquired infection from the inoculating sporozoites, are resistant to these drugs. This resistance may be either by these forms possessing pathways of me-

tabolism alternate to those interruptable by the drug in the erythrocytic forms, or by their lacking the ability to concentrate the drug from the surrounding medium in effective amounts. Experiments with avian malaria have shown the existence of pre-erythrocytic forms of the parasites (cryptozoites), as well as other types of exo-erythrocytic forms, but these have never been conclusively demonstrated in man.

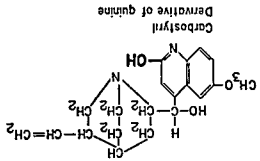
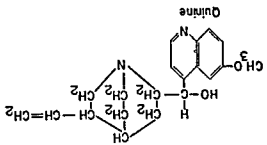
## QUININE

*Quinine is the chief alkaloid in cinchona bark. It was first isolated by Pelletier and Caventou in 1827 and has recently been prepared synthetically but the procedure is economically impractical. The metabolism and the therapeutic effectiveness of the four predominant cinchona alkaloids—quinine, quinidine, cinchonine and cinchonidine—is essentially the same except for the slightly greater rate of degradation of cinchonidine in the human body with resultant lower blood concentrations. A relatively crude preparation of cinchona bark, containing all four of these alkaloids, is available under the name "Totaquine." It has no advantage over the pure alkaloids except its lower cost.*

Quinine is rapidly absorbed from the gastro-intestinal tract or from intramuscular injection. It may be used intravenously if given slowly and in high dilution. Intramuscular injections may be followed by painful sterile abscess formation, and cardiovascular collapse has resulted from its intravenous use. Therefore, it should be given by the oral route unless the patient is moribund or for some reason unable to absorb the drug.

Animal experiments indicate that quinine is distributed very unevenly in the body. The liver, spleen, lung and kidney concentrate the drug in highest amounts. The blood, muscle and nervous tissue retain relatively little of it. Plasma and red blood cells contain approximately equal amounts, but the white blood cells concentrate the drug to from two to ten times the plasma value. Urinary excre-

tion accounts for less than 10 per cent of the administered dose. At least part of the remaining 90 per cent is oxidized in the liver to the carboxtyril derivative, which is then excreted in the urine. It is only about one third as active as quinine in experimental malaria but is correspondingly less toxic.

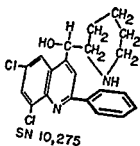


Derivative of quinine

The establishment of the chemical structure of this metabolite of quinine suggested the synthesis of analogous compounds in which the susceptible point of oxidation would be blocked by the addition of a more resistant group. Such compounds are still in the developmental stage but some of them show greatly enhanced activity against experimental malaria. One of these, SN 10,275, is retained by the body approximately fifty times as long as quinine.

The rapid metabolism of quinine makes it a noncumulative drug. Consequently, full antimalarial action (with plasma concentrations of 5 mg. (1 liter or higher) can be obtained early in the course of treatment. Maintenance of this action requires frequent administration of the drug,

optimal results being obtained when the drug is given every 4 hours. The dosage schedule does not have to be lowered during the course of treatment and toxic symptoms can be quickly alleviated by cessation of administration of the drug. These toxic symptoms are collectively known as "cinchonism" and consist of ringing in the ears, headache, blurred vision, photophobia, edema and skin rash. Idiosyncrasy to quinine is not uncommon. High doses of quinine have been known to cause blindness (quinine amblyopia), apparently due to a spasm of the retinal arterioles.



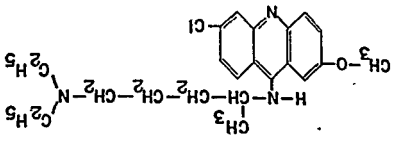
Quinine has a central antipyretic effect and was formerly widely used as an antipyretic. It has some chemotherapeutic action in bacterial infections but is little used in these conditions because of its inefficacy and its unpleasant side actions. Ethylhydrocupreine (optochin), a synthetic compound closely related to quinine, was shown by Morgenroth in 1911 to be effective against pneumococcal infections. Its systemic use was abandoned when it was found to cause damage to the optic nerve, though it may be applied locally in the treatment of pneumococcal infections of the eye. Hydroxyethylapocupreine is a much less toxic compound and might have found wide use in the treatment of pneumonia but for the advent of the more effective sulfonamides.

Quinine has a curare-like action on skeletal muscle (see Chapter 5) and like curare has been used for the diagnosis of myasthenia gravis since small doses accentuate the con-

dition. It is of questionable value in the relief of spastic conditions.

Quinine may occasionally give dramatic relief of itching, its mode of action being unknown. The oxytocic action of quinine is discussed in Chapter 19 and its local anesthetic action in Chapter 6. The use of quinine as a heart drug is discussed in Chapter 14. Quinidine is rarely used in malaria though it is of some value in patients sensitive to quinine. Until recently, quinine was the drug of choice for the treatment of all types of malaria. Its low toxicity and its relative abundance, coupled with its long history of usefulness, assure its continuation as a valuable adjunct. Newer drugs, especially quinacrine, chloroquine and paludrine are superior in many respects but their toxic potentialities are not so thoroughly understood and their very newness militates against their complete acceptance. However, malignant tertian malaria, caused by *P. falciparum*, yields completely to these newer drugs, whereas quinine is of relatively little value in this infection. Blackwater fever, a common complication of falciparum malaria, seems to occur infrequently when the infection is treated promptly and adequately with quinacrine, chloroquine or paludrine.

### QUINACRINE



Quinacrine (mepacrine, atabrine) is a yellow-orange alkaloid whose acid salts are freely soluble in water. The drug is almost invariably given by mouth since its parenteral use may be accompanied by local irritation at the site of injection.



tion, or by syncope if it is given intravenously. When given by mouth, gastric irritation may be severe, leading to nausea and vomiting. This is best controlled by giving the drug after meals.

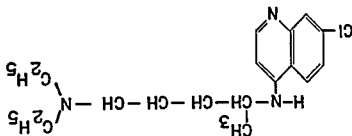
Quinacrine is rapidly absorbed from the intestinal tract and is stored in the tissues for a considerable period. Distribution of the drug in the body is very uneven, more or less paralleling that of quinine except that blood and plasma concentrations are very low. Suppression of the early signs and symptoms of the disease is usually obtained with a concentration of 25  $\mu$ g. of quinacrine per liter of plasma, requiring the daily administration of 0.1 Gm. of quinacrine hydrochloride. Since the concentration of this drug in the white blood cells is several hundred times that of the plasma, analyses obtained with whole blood are apt to give misleading results.

Quinacrine is a cumulative drug. Less than 5 per cent of the administered drug is excreted, although traces of the drug can be found in the urine for 1 or 2 months after the last dose. Quinacrine is deposited in the skin and nails, persisting for weeks or months after discontinuance of the drug. This slow excretion and metabolism account for the accumulation of the drug in the body during a period of continual administration and explain the necessity for large initial doses in order to achieve full suppressive or therapeutic effects as early as possible. For the treatment of an acute attack, usually 1.0 Gm. of quinacrine hydrochloride is given in divided doses the first day, followed by 0.3 Gm. per day for 6 days.

Quinacrine is remarkably free from serious toxic effects, although it may produce several minor or subjective symptoms. The yellow pigmentation of the skin, due to the deposition of quinacrine or its metabolites and not to jaundice, is cosmetically undesirable. Gastro-intestinal upsets, with nausea or vomiting and diarrhea, are not uncommon. Manifestations of allergic reactions may be encoun-

tered, but these are rarely of sufficient severity to warrant withdrawal of the drug. Toxic psychoses, aplastic anemia and atypical lichen planus are other relatively infrequent complications.

### CHLOROQUINE



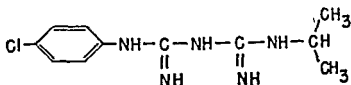
Chloroquine (SN7618) was introduced in 1944. Absorption of this drug from the gastro-intestinal tract is rapid and complete and from 10 to 20 per cent of the total dose is excreted in the urine. Chloroquine is as persistent in the body as quinacrine but exerts a suppressive action with a plasma concentration as low as 5 to 8 µg. per liter, thus permitting adequate suppression of the symptoms of the disease with a dosage schedule of only one dose of 500 mg. or less of chloroquine diphosphate per week. Chloroquine provides the most rapid rate of parasite clearance from the blood and the longest latent period between attacks. It also has the advantage of being a colorless compound and thus does not cause the yellow pigmentation of the skin caused by quinacrine. Chloroquine may produce the same signs and symptoms of toxicity as quinacrine, but their incidence is less. Mild pruritus may also occur.

### PALUDRINE

Paludrine was introduced in 1945 by a group of English investigators. It has a suppressive action similar to that of quinine, quinacrine and chloroquine with the further advantage of exceptionally low toxicity and cheapness of manufacture. Its action is less rapid than that of the other sup-

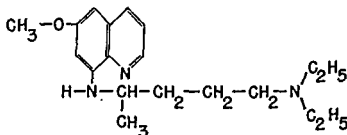
pressive drugs, full suppression of the disease being not ordinarily obtained for 3 or 4 days after treatment is begun. The usual therapeutic dose is 100 mg. per day; however, doses of 1000 mg. produce no signs or symptoms of toxicity.

Paludrine is readily absorbed following oral administration. About one third of the dose is excreted through the



bile and the intestinal mucosa and appears in the feces. A smaller amount is excreted in the urine. The drug is not cumulative with ordinary doses; however, weekly administration of the drug seems adequate to suppress infections. Like quinacrine and chloroquine, it is a curative agent in *P. falciparum* infections but is without effect on the relapse rate in *P. vivax* infections. Hawking has shown that paludrine per se is inactive; it is converted in the body to an unknown metabolite which is the active antimalarial agent.

### PAMAQUINE



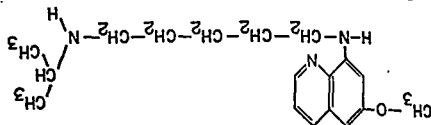
Pamaquine was introduced by Fischl in 1926 as the result of the study of thousands of compounds in experimental avian malaria. The chemotherapeutic index of this compound, in birds indicated that it would be a most valuable and safe drug; unfortunately, it proved to possess unexpectedly high toxicity in mammals, including man. It found

some use, however, in the public-health aspects of malaria, since it has a peculiar gametocidal effect in low, relatively nontoxic doses which are ineffective against the asexual-forms which are responsible for the symptoms and continuation of the disease in man. Thus, the effective use of the drug in all infected human beings within a given area would prevent the infection of the mosquito vectors and therefore limit the spread of the disease. Although theoretically possible, this procedure is impractical except in rare instances, such as under military control.

Pamaquine appears to have a definite effect in lowering the relapse rate in *P. vivax* infections when it is given in dangerously high doses and in conjunction with quinine. The toxic effects so produced are usually so serious as to prevent this use of the drug but nevertheless it was the first drug, and until the discovery of pentaquine the only one possessing any curative action in *P. vivax* infections.

The absorption, intermediary metabolism, excretion, usage and toxic symptoms of pamaquine are essentially the same as those of pentaquine. It is now certain that pamaquine will be completely replaced by pentaquine or one of its analogues.

### PENTAQUINE



Many hundreds of compounds related to pamaquine have been synthesized and tested in the search for a less toxic agent which might retain the curative power of pamaquine. At present, the most promising of these analogues is pentaquine (SN13,276). A given dose of pentaquine is about half as toxic, and half again more active, than the same dose of

pamaquine. This improvement in the chemotherapeutic ratio is sufficient to make the drug a most useful addition to our list of antimalarial agents. From 40 to 80 mg. of pentaquine monophosphate is the daily dose; the lower amount almost never produces toxic symptoms and is very effective in producing a complete cure in old cases of *P. vivax* infections which have been kept under control with one of the suppressive drugs.

Pentaquine is always used with quinine. It has now been demonstrated experimentally as well as clinically that there is a definite synergistic response to the administration of a combination of these drugs. Pentaquine is always given by mouth and it is rapidly and completely absorbed from the intestinal tract. It is not a cumulative drug but the nature and extent of its degradation in the body is not known. Only small amounts are excreted. The usual course of treatment is 14 days. A second or third course may be necessary in recent heavy infections.

The toxic symptoms of pentaquine include abdominal pain with nausea and anorexia, anemia, leukopenia, fever, cyanosis due to methemoglobinemia, and jaundice. Acute intravascular hemolysis, long, persistent postural hypotension and syncope may occur at dosage levels of 180 mg. of pentaquine monophosphate per day. There is some evidence of a synergism in toxic action with the development of agranulocytosis when pentaquine and the sulfonamides are used concurrently.

### PREPARATIONS

Quinine bisulfate U.S.P.; B.P. 1 Gm.

Quinine bisulfate tablets U.S.P.

Quinine dihydrochloride U.S.P.; B.P. 1 Gm.

Quinine hydrochloride U.S.P.; B.P. 0.6 Gm.

Tablets of quinine hydrochloride B.P. 0.6 Gm.

Quinine sulfate U.S.P.; B.P.

Quinine-sulfate tablets U.S.P. Usually 0.12, 0.2 and 0.3 Gm. tablets.

Totaguine U.S.P. A mixture of cinchona alkaloids containing not less than 10 per cent anhydrous quinine and between 70 and 80 per cent of total anhydrous crystallizable cinchona alkaloids. 0.6 Gm.

Totaguine capsules U.S.P. Usually 120, 200 and 300 mg. capsules.

Totaguine tablets U.S.P. Usually 120, 200 and 300 mg. tablets.

Quinacrine hydrochloride U.S.P. Mepacrin hydrochloride B.P. 0.1 Gm.

Quinacrine-hydrochloride tablets U.S.P. Usually 50 and 100 mg. tablets.

Mepacrine methanesulphonate B.P. 0.05 to 0.1 Gm. intramuscular.

Pamaquine B.P. 0.025 to 0.05 Gm.

## BIBLIOGRAPHY

Series of papers on clinical studies on quinacrine, chloroquine, paludrine and pentaquine, special number of J. Clin. Investigation (in press, fall, 1947).

Bang, F. B., N. G. Hairston, W. Trager and J. Maier: Treatment of acute attacks of vivax and falciparum malaria: A comparison of atabrine and quinine, Bull. U. S. Army M. Dept. 7: 75, 1947.

Butler, M. G.: Atypical lichen planus tropicalis, Arch. Dermat. & Syph. 55: 535, 1947.

Fitzhugh, O. G., A. A. Nelson and H. O. Calvery: Chronic toxicity of quinacrine, J. Pharmacol. & Exper. Therap. 85: 207, 1945.

Hawking, F.: Activation of paludrine in vitro, Nature 159: 409, 1947.

Kelsey, F. E., F. K. Oldham, W. Cantrell and E. M. K. Gelling: Antimalarial activity and toxicity of a metabolic derivative of quinine, Nature 157: 440, 1946.

- Kelsey, F. E., F. K. Oldham and E. M. K. Geiling: Studies on antimalarial drugs—the metabolism of quinine and quinidine in birds and mammals, *J. Pharmacol. & Exper. Therap.* 85: 170, 1945.
- Loeb, R. F.: Activity of a new antimalarial agent, chloroquine (SN7,618), *J.A.M.A.* 130: 1069, 1946.
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- Wiselogle, F. Y.: A Survey of Antimalarial Drugs, 1941-1945, Ann Arbor, Mich., Edwards, 1946.

The antibacterial activity of sulfanilamide was first observed by the Tréfouels in Fournau's laboratory in France in 1935. This finding resulted from a study of the intermediary metabolism of the recently announced dyestuff "prontosil," which had been synthesized in 1932 and was shown by Domagk early in 1935 to have a remarkable curative effect in experimental hemolytic streptococcal infections in mice.

The discovery of the activity of the sulfonamide drugs gave the first real impetus to the study of chemotherapy since the work of Paul Ehrlich. The lack of success in the search for active antibacterial agents had slowly built up a philosophy that bacteria, being relatively simple forms of life, could never be expected to respond to chemotherapy as completely as the more complex parasitic micro-organisms. Since 1935, developments in the field of bacterial chemotherapy have been rapid. Not only have many new and important therapeutic agents been introduced but also considerable progress has been made in understanding the mechanism of action of these drugs. In a few isolated cases, these new theories have been responsible for the synthesis of new and active drugs and further progress may be expected to yield even more important chemotherapeutic agents.

## INTRODUCTION

### PREPARATIONS

MISCELLANEOUS SULFONAMIDES

SULFADIAZINE

SULFATHIAZOLE

INTRODUCTION

# Sulfonamides



- Kelsey, F. E., F. K. Oldham and E. M. K. Geiling: *Studies on antimalarial drugs—the metabolism of quinine and quinidine in birds and mammals*, J. Pharmacol. & Exper. Therap. 85: 170, 1945.
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dation of the chemical structure of pteroylglutamic acid, and the proof that it contains p-aminobenzoic acid, it was suggested that the reaction which is inhibited by the sulfonamides might be the synthesis of pteroylglutamic acid from its components. In substantiation of this hypothesis, it has been observed that certain micro-organisms which require pteroylglutamic acid as a growth factor are unaffected by the sulfonamides.

The variations in activity among the sulfonamides may be explained in several ways. First, substitutions in the acid amide portion of the molecule so affect the electronegative characteristics of the acid group that the resulting compound is more nearly identical, from the standpoint of ionization characteristics, to p-aminobenzoic acid. Second, these substituting groups may potentiate the activity by competing with other "essential metabolites" in enzymatic reactions, as, for example, sulfathiazole with riboflavin, sulfapyridine with niacin, and sulfadiazine with thiamine. Finally, differences in the clinical usefulness of these compounds is dependent largely on such factors as solubility of the drug and its metabolic products, distribution in the tissues of the body, inactivation by adsorption on blood and tissue proteins and the rate of excretion of the drug. There is also sufficient variation in the toxicity of these drugs to warrant special consideration of possible toxic reactions with each individual drug. Thus, the choice of a sulfonamide may vary not only from one infection to another, but also from patient to patient. Too much emphasis cannot be placed on the necessity for careful examination of the patient before these drugs are prescribed.

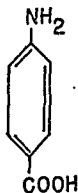
Sensitization and Developed Resistance. Indiscriminate or too frequent use of the sulfonamide drugs may lead to the development of an allergic type of reaction whereby skin rashes, photosensitivity or, more rarely, acute granulocytopenia or anemia may result from subsequent use of the drug. Furthermore, it is becoming increasingly evident that the

**Mechanism of Action.** The sulfonamides are active bacteriostatic agents in infections produced by a variety of bacteria, including hemolytic streptococci, meningococci, gonococci, pneumococci, staphylococci and *H. influenzae*.

Soon after the discovery of the antibacterial activity of the sulfonamides, it was found that the extracts of bacterial cultures, or yeast, contain a substance capable of neutralizing the effect of these drugs. This substance was shown



Sulfanilamide



P-aminobenzoic acid

by Woods in 1940 to be p-aminobenzoic acid. The close structural relationships between these two compounds suggested a possible mechanism of action. If it be supposed that p-aminobenzoic acid is an "essential metabolite," i.e., required by the cell for its continued growth and multiplication, then the presence of sulfanilamide or one of its derivatives in the media would tend to block, by competitive inhibition, the reaction utilizing p-aminobenzoic acid. It has since been shown that p-aminobenzoic acid is required for the growth of certain micro-organisms and is present in most, if not all, living cells. Following the eluci-

be determined by chemical analysis. Urinary analysis may be necessary in new patients before the administration of the priming dose in order to determine whether or not the patient may have been receiving one of these drugs in the recent past and accordingly does not need, and may not be able to tolerate, a large initial dose.

TABLE 7

INFLUENCE OF pH ON SULFONAMIDE SOLUBILITY

SULFONAMIDE		SOLUBILITY, AS MG.%, IN AQUEOUS BUFFER SOLUTIONS		
		pH 5.5	pH 6.5	pH 7.5
Sulfathiazole	98	108	235	29
Acetylsulfathiazole	7	13	28	200
Sulfadiazine	13	20	75	512
Acetylsulfadiazine	20	35	45	170
Sulfamerazine	35	38	57	272
Acetylsulfamerazine	38	69	76	140
Sulfamethazine	69	90	107	240
Acetylsulfamethazine	90			

Modified from D. R. Gilligan, S. Garb, C. Wheeler and N. Plummer: J. A. M. A. 122: 1160, 1943.

Generally speaking, the sulfonamides are eliminated from the body through the urine. The rapid rate of excretion, the relatively large amounts involved, and the low aqueous solubility, all tend to favor precipitation of microcrystals of these drugs in the kidney tubules. This crystalluria is the most frequent hazard encountered in sulfonamide therapy. In those few cases in which actual blockage of the tubules occurs, death may result from kidney damage and anuria. The solubility of the sulfonamides and of their metabolic products is greatly increased in slightly alkaline solutions (see Table 7). This prompted the formerly widespread practice of administration of sodium bicarbonate along

*inadequate use of one of these drugs in a given infection tends to result in the appearance of a strain of the infecting organism which is resistant to further treatment with the drug and which is also frequently possessed of even greater virulence than the original strain. For these reasons, the use of the sulfonamides either in the local treatment of wounds and burns or for routine prophylaxis is to be condemned.*

Certain strains of generally susceptible bacteria are found to be less sensitive than others to the action of the sulfonamides. In some cases, these may be examples of developed resistance, while in others, where there is no possibility of previous exposure of the bacteria to the drug, the resistance must be natural, not acquired. The detection of sulfonamide resistance, and an approximation of its magnitude, can be made in the laboratory, and such tests should be made in all cases in which the drug fails to suppress the infection within 3 or 4 days of adequate administration.

**Metabolism.** With certain exceptions, the sulfonamides are rapidly absorbed when given by mouth. These drugs are all relatively insoluble in water but for parenteral administration the sodium salts may be used. Highly concentrated solutions may be so obtained but the high alkalinity (pH 10 or above) makes them too irritant except for intravenous use.

In order to exert a maximal effect on the invading organisms, the decision to use one or more of the sulfonamides in a given case should be implemented by the administration of a large "priming" dose in order to more or less saturate the body with the drug. This should be followed by regular day and night doses at whatever intervals may be required to maintain a relatively constant concentration of the drug in the blood and tissues. The size of the initial dose and the frequency of maintenance doses will vary according to the rate of excretion of the drug. This is reflected by the blood concentrations of the drug which can

which may be of special importance to ambulatory patients; painful joints, cyanosis, acidosis, mild hemolytic anemia and hematuria. Drug rash or drug fever may also occur. Drug fever is sometimes hard to detect since its onset may be simultaneous with the decrease in fever resulting from the suppression of the infecting organisms by the drug. The more serious signs and symptoms include leukopenia with granulocytopenia, acute hemolytic anemia, anemia with azotemia, leukocytosis, purpura hemorrhagica and jaundice. None of the toxic manifestations seem to be influenced by the administration of p-aminobenzoic acid; the treatment is based on measures designed to increase the amount of urine formation in order to prevent kidney damage and to aid in the excretion, and such supportive measures as may be indicated.

## SULFATHIAZOLE

At the present time, the choice of a sulfonamide usually lies between sulfathiazole and sulfadiazine. Sulfathiazole was first synthesized in a number of laboratories in 1939. It is much more effective than the earlier sulfanilamide or sulfapyridine. It is the sulfonamide of choice in the treatment of mixed infections since it appears to be active against a greater variety of organisms. It is also thought to be more active than sulfadiazine and its homologues in staphylococcal and gonococcal infections. This may or may not be true; in any case, penicillin is now the drug of choice for these infections. Sulfathiazole has been widely used as a urinary-tract antiseptic because of its polyvalent action and its rapid urinary excretion.

The metabolism of sulfathiazole is characterized by rapid absorption and excretion. The initial dose is usually from 4 to 6 grams, subsequent maintenance doses are 1 gram given at least every 4 hours. This is usually adequate, but it can be increased if due regard is taken of the poor solubility of this drug in the urine.

with the drug in order to alkalinize the urine. Clinical experience, however, has shown that easily tolerated amounts of bicarbonate do not actually influence the acidity of the urine sufficiently to affect the solubility of the drugs. In practice, maintenance of a large volume of fluid output is the method of choice. The volume of urine excreted per day should be kept over 1,500 cc. This may be difficult to obtain in moribund patients, in patients with diarrhea, or in very warm climates. Recently the practice has been introduced of giving two or more of the sulfonamide drugs at the same time, since a saturated solution of such a mixture contains considerably more sulfonamide than a saturated solution of either drug alone.

The only chemical changes that are made in the sulfonamide molecules to any extent by the body are referable to the *p*-amino group. This may be esterified, usually with an acetate group, resulting in the formation of an acetylsulfonamide. This is of practical importance because the acetyl derivative is without therapeutic effect, yet its solubility in urine may be either more (e.g., acetylsulfadiazine) or less (e.g., acetylsulfathiazole) than that of the parent compound. The degree of acetylation varies from one species of animal to another as well as from one drug to another.

**Toxic Effects.** The sulfonamides are one of the most important groups of therapeutic agents but they are not without serious toxic potentialities. In addition to the possibilities of drug sensitization and kidney damage already discussed, there is a group of minor or moderately severe signs and symptoms which may occur but which do not call for stopping further administration, as well as a group of more severe signs and symptoms which demand immediate measures as well as a careful evaluation as to whether the disease or the drug presents the greater hazard to the patient. In the first group are nausea and vomiting, with or without stomatitis, abdominal cramps, flatulence or diarrhea; dizziness, psychoses, ocular and auditory disturbances,

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This adsorption, however, appears to be readily reversible, since the drug is completely excreted by the kidney within 24 hours after the last dose. This rapid clearance is an advantage in those cases in which severe toxic symptoms suddenly appear.

The incidence of toxic reactions to sulfathiazole is generally higher than is the case with sulfadiazine. Nausea occurs in about one third of the cases and allergic manifestations, such as skin eruptions (from 8 to 10 per cent), drug fever (from 5 to 6 per cent), and conjunctivitis (4 per cent), are more frequent with sulfathiazole than with any other commonly used sulfonamide. Special precautions must be taken to insure an adequate flow of urine because of the low solubility of the drug.

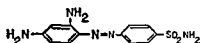
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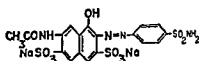
In addition to its relatively low toxicity, sulfadiazine offers the convenience of longer persistence in the body, making the maintenance of constant blood levels of the drug somewhat easier. As with all the sulfonamides, a priming dose is necessary (from 2 to 4 grams) with maintenance doses of 1 gram every 4 to 6 hours. A blood concentration of 15 mg. per cent or higher is desirable in severe infections, while one of from 5 to 10 mg. per cent is usually satisfactory in mild infections. The drug is not completely absorbed from the intestinal tract but the fraction that is absorbed, from 60 to 80 per cent, is quite constant. It diffuses into the spinal fluid in concentrations of from 50 to 75 per cent of the blood level, and into pleural and ascitic fluid in con-

Sulfathiazole is fairly evenly distributed in the body tissues with the exception of the cerebrospinal fluid, where the concentration attained is only 10 per cent that of the blood. The high activity of orally administered sulfathiazole in meningitis suggests, however, that penetration of the drug

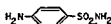
## Sulfonamides



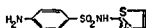
Prontosil



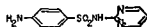
Neo-prontosil



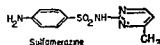
Sulfanilamide



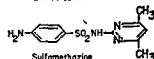
Sulfathiazole



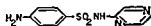
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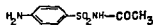
Sulfamerazine



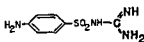
Sulfamethazine



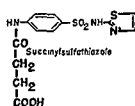
Sulfapyrazine



Sulfacetamide



Sulfaguanidine



Succinylsulfathiazole

is somehow increased when the meninges are infected, as has been shown in the case of penicillin.

In man, the amount of sulfathiazole in the blood and in the urine in the acetylated form is from 10 to 30 per cent. From 60 to 80 per cent of the total unacetylated drug present in the plasma may be adsorbed on the plasma albumins.

This adsorption, however, appears to be readily reversible, since the drug is completely excreted by the kidney within 24 hours after the last dose. This rapid clearance is an advantage in those cases in which severe toxic symptoms suddenly appear.

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centrations of from 60 to 80 per cent of the blood level. The concentration attained in the tissues is approximately equal to that of the blood. From 1 to 20 per cent of the blood sulfadiazine is acetylated and from 20 to 40 per cent of the urinary sulfonamide is acetylated, indicating partial tubular reabsorption of the free drug. About half of the sulfadiazine present in the blood is adsorbed on the plasma albumins. Excretion is complete after from 48 to 72 hours.

Although acetylsulfadiazine is more soluble than acetylsulfathiazole, the relative solubilities of the parent compounds are reversed (see Table 7). The chief disadvantage of sulfadiazine is this low solubility, since it favors the production of concretions in the kidney. A large number of compounds have been synthesized and studied in an attempt to find one retaining the high effectiveness and low toxicity of sulfadiazine but with a greater solubility. These researches have been partly successful, but the problem is actually of little importance as long as a large fluid output can be maintained.

All the toxic manifestations of the sulfonamides, as a class, have been reported following the use of sulfadiazine. Although the incidence is quite low, several deaths have been reported in the literature and precautionary measures should be taken with every patient receiving a long course or a relatively high dosage schedule.

### MISCELLANEOUS SULFONAMIDES

Thousands of compounds have been synthesized for study in this field. Some have had brief periods of popularity in the past and are now almost completely discarded. Others are still in an investigative phase and may well supplant the currently used ones as further experience is gained. The compounds discussed in this section are examples of both categories.

Prontosil is the complex organic dye reported by Domagk in 1935 to be effective against hemolytic streptococcal infections. This patented preparation was used widely in the months immediately following this announcement but its use was greatly curtailed by the discovery that sulfanilamide was the active portion of the molecule. A derivative of prontosil, neo-prontosil (Prontosil-S, Azosulfamide) offers the distinct advantage of being freely water-soluble. It is perhaps unfortunate that patent restrictions on this class of compounds prevented further investigations of their properties and therapeutic values. Prontosil is not an official drug and finds little or no use today in the United States. Sulfanilamide is the least active of the sulfonamides. Its one advantage is that it has relatively high solubility in water. Saturated aqueous solutions contain approximately 800 mg. per cent at 25° C., while human serum at 37° C. can hold in solution nearly 2,000 mg. per cent. The drug is almost never used today for systemic administration. Its use for local application, originally promoted because of the ease with which high local concentrations could be secured, is gradually falling into disfavor because of the danger of inducing sensitization in the host and resistance in the infecting organisms.

Sulfapyridine was introduced by Whitty in England in 1937, particularly for the treatment of pneumonia. It is irregularly and often poorly absorbed from the intestinal tract. Excretion is slow and from 4 to 5 days may be required for its complete elimination. The incidence of nausea and vomiting and anemia is greatest with sulfapyridine. The erratic absorption and the high toxicity of this drug has resulted in its almost complete replacement by other sulfonamides.

Sulfamerazine (sulfamethyldiazine) has much the same properties as sulfadiazine. It has the advantage of greater solubility, especially in acid urine, and thus is less apt to cause kidney damage. It is more rapidly absorbed and more

slowly excreted, thus giving higher and more prolonged blood levels and need only be given at 8- rather than at 4- or 6-hour intervals as is the case with sulfadiazine.

Sulfamethazine (sulfadimethyldiazine) is almost identical in its action to sulfamerazine except that its solubility in acid urine is even greater. Neither of these methyl derivatives has received nearly as much clinical trial as sulfadiazine, but there is some evidence that, despite their greater solubility, kidney damage may occur.

Sulfapyrazine is an isomer of sulfadiazine. Its absorption from the intestinal tract is limited. With small doses, almost complete absorption occurs while larger doses do not give proportionately higher blood levels, thus affording an automatic safety mechanism against overdosage. The activity and toxicity of sulfapyrazine approximates that of sulfadiazine.

Sulfacetamide is used as a urinary-tract antiseptic. Absorption and excretion are rapid and complete. Since tubular reabsorption is negligible, high concentrations are easily obtained in the urine with relatively low, nontoxic doses. The antibacterial activity is not as great as that of sulfathiazole in equivalent concentrations; however, the high, safe concentrations readily obtained with sulfacetamide (from 50 to 100 mg. per cent) are as effective, if not more so, than the lower safe concentrations of sulfathiazole (from 5 to 10 mg. per cent).

The drug is about fifteen times as soluble in water as sulfathiazole and about one hundred fifteen times as soluble as sulfadiazine; consequently, intrarenal precipitation does not occur. Furthermore, sulfacetamide has the advantage of being sufficiently soluble even in acid urine to permit its use with such acidifying agents as may be desirable to maintain the necessary degree of urinary acidity for optimal antibacterial action.

Sulfaguanidine was introduced in 1940 by Marshall and his associates as an intestinal antiseptic. Its absorption from

the intestinal tract is relatively poor; hence, it exerts a high degree of local antibacterial action. However, sufficient absorption may occur to produce severe toxic effects, especially when the drug is used under conditions which prevent the maintenance of high urinary volumes. The drug offers no special advantages over succinylsulfathiazole or sulfathiazole as an intestinal antiseptic.

Succinylsulfathiazole (sulfasuxidine) is not absorbed from the intestinal tract in significant amounts. Accordingly, it is only used in the treatment of infections of the intestinal tract. In itself it is almost without antibacterial activity; however, a small fraction is slowly hydrolyzed to give free sulfathiazole, which is the active antibacterial agent. The dosage of succinylsulfathiazole is very large; from 20 to 60 grams may be given at intervals of 4 hours for several days. It is gradually being supplanted by sulfathiazole used as such, since the effectiveness is about the same and much smaller doses are required.

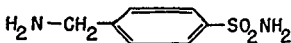
Sulfamylon (marfanil, homosulfanilamide, mesudin, sulfabenzamine) is a sulfonamide which is superficially very similar in structure to sulfanilamide. However, the pharmacologic properties of the two compounds are quite different. The antibacterial activity of sulfamylon is not affected by the addition of p-aminobenzoic acid to the medium nor is it affected by the presence of pus or necrotic tissue. It is recommended in the German literature for use in the local treatment of wounds when mixed with nine parts of sulfanilamide where it may be of value against *Clostridium welchii* and *Cl. septicum*, and against streptococcal strains which are resistant to ordinary sulfonamides.

Sulfamylon is of no value for systemic administration because of its extremely rapid excretion in the urine. It is freely soluble in water. No toxic symptoms have been reported following its use.

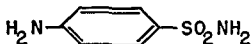
Sulfonamide or Antibiotic? The question of whether to use sulfonamides or antibiotics for the treatment of infec-



tion which are amenable to both is frequently difficult to answer. The chief advantages offered by the sulfonamides are oral administration, a slightly longer history of successful clinical use and considerably less expense. The anti-



### Sulfamylon



### Sulfanilamide

biotics offer the advantages of generally greater activity with negligible toxic effects. Both classes of drugs have been introduced too recently to permit a complete and final evaluation of their relative merits.

### PREPARATIONS

Sulfathiazole U.S.P. 2 Gm.

Sulfthiazole tablets U.S.P.; B.P. Usually 300 mg. and 500 mg. tablets.

Sulfathiazole sodium U.S.P.; B.P. 2 Gm.

Sterile sulfathiazole sodium U.S.P. 2 Gm. intravenous.

Sulfadiazine U.S.P.; B.P. 2 Gm.

Sulfadiazine tablets U.S.P.; B.P. Usually 300 mg. and 500 mg. tablets.

Sulfadiazine sodium U.S.P.; B.P. 2 Gm.

Sterile sulfadiazine sodium U.S.P. 2 Gm. intravenous.

Sulfanilamide U.S.P.; B.P. 2 Gm.

Sulfanilamide tablets U.S.P.; B.P. Usually 300 mg. and 500 mg. tablets.  
 Sulfapyridine N.N.R.; B.P. Tablets of sulphapyridine B.P.  
 Soluble sulfapyridine B.P.  
 Sulfamerazine U.S.P. 2 Gm.  
 Sulfamerazine tablets U.S.P. Usually 0.5 Gm. tablets.  
 Sterile sulfamerazine sodium U.S.P. 2 Gm. intravenous.  
 Sulfapyrazine N.N.R.  
 Sulphacetamide B.P.  
 Soluble sulphacetamide B.P.  
 Sulfguanidine U.S.P.; B.P. 2 Gm.  
 Sulfguanidine tablets U.S.P.; B.P. Usually 300 mg. and 500 mg. tablets.  
 Succinylsulfathiazole U.S.P. 2 Gm.  
 Succinylsulfathiazole tablets U.S.P. Usually 300 mg. and 500 mg. tablets.

## BIBLIOGRAPHY

Council report: Dangers from the external use of sulfonamides, J.A.M.A. 128: 1024, 1945.  
 Beyer, K. H., H. F. Russo, E. A. Patch, L. Peters and K. L. Sprague: The formation and excretion of acetylated sulfonamides, J. Lab. & Clin. Med. 31: 65, 1946.  
 Bratton, A. C., and E. K. Marshall, Jr.: A new coupling component for sulfanilamide determination, J. Biol. Chem. 128: 537, 1939.  
 Collins, E. N., and J. S. Hewlett: Succinylsulfathiazole (sulfasuxidine) in treatment of chronic ulcerative colitis: Report 55 cases followed two years; its value by retention enema in early cases, Gastroenterology 7: 549, 1946.  
 Dowling, H. F., H. L. Hirsch and M. H. Lepper: Toxic reactions accompanying second courses of sulfonamides in patients developing toxic reactions during a previous course, Ann. Int. Med. 24: 629, 1946.  
 Dowling, H. F., H. H. Hussey, H. L. Hirsch and F. Wilhelm: Penicillin and sulfadiazine compared with sulfadiazine alone, in treatment of pneumococcic pneumonia, Ann. Int. Med. 25: 950, 1946.

- Frisk, A. R., G. Hagerman, S. Helander and B. Sjögren: "Sulpha-combination"—A new chemotherapeutic principle, *Brit. M. J.* 1:7, 1947.
- Gilligan, D. R.: Comparative studies of the chemical changes occurring in sulfonamide drugs during therapy in man, *J. Clin. Investigation* 24:301, 1945.
- Grand, M. J. H., J. B. Stanbury, E. W. Ekermeier and J. D. Purvis, Jr.: Rheumatic fever: statistical analysis of incidence during sulfadiazine prophylaxis, *U. S. Nav. Med. Bull.* 46<sup>2</sup>:1793, 1946.
- Kracke, R. R.: The effects of sulfonamide drugs on the blood, *Am. J. Clin. Path.* 14:191, 1944.
- Lees, R.: Treatment of sulphonamide-resistant gonorrhoea with penicillin, *Brit. M. J.* 1:605, 1946.
- Mitchell, G. A. G., W. S. Rees and C. N. Robinson: Marfanil and marfanil prontosil, *Lancet* 1:627, 1944.
- O'Donnell, C. H., J. L. Posch and J. W. Hirshfeld: A study of the values of local sulfathiazole in operative wounds in the prophylaxis of infection, *Surg. Gynec. & Obst.* 82:323, 1946.
- Rothman, P. E.: Recurrence of infection following therapy with sulfonamide compounds and penicillin, *Am. J. Dis. Child.* 72:415, 1946.
- Woolley, D. W.: Recent advances in the study of biological competition between structurally related compounds, *Physiol. Rev.* 27:308, 1947.

# Antibiotics

INTRODUCTION	TYROTHRICIN
PENICILLIN	BACITRACIN
STREPTOMYCIN	MISCELLANEOUS ANTIBIOTICS
	PREPARATIONS

## INTRODUCTION

In its broadest sense, the term "antibiotic" describes any substance capable of destroying life or living matter. However, it is now generally used in a more restricted sense to describe antimicrobial agents produced by molds, bacteria or actinomycetes. The present chapter deals with antibiotic agents of established therapeutic value.

The development of antibiotics as chemotherapeutic agents may be said to have been initiated by the English bacteriologist Alexander Fleming in 1929, although from the time of Pasteur sporadic attempts were made to utilize as a therapeutic weapon the known antagonism between certain micro-organisms. Fleming, while studying staphylococcus variants, noted a transparent zone surrounding a mold contaminant of a culture plate of staphylococcus. Properly interpreting this clear zone as evidence of lysis of the bacteria by a diffusible substance produced by the mold, he prepared cell-free filtrates of broth cultures of this mold and demonstrated their antibacterial activity. The activity was lost so rapidly from the filtrate that he was unable to obtain adequate quantities for complete studies; however, he did demonstrate the relatively low toxicity of the substance and its activity against a number of pathogenic bacteria. Since the mold belonged to the genus *Penicillium*, he adopted the name "penicillin" for the active

agent in the filtrates. In 1940, Florey and his associates were able to produce stable preparations of penicillin by sterilizing a neutralized filtrate and were thus able to proceed with more extensive experimental laboratory and clinical investigations. Meanwhile, in 1939, Dubos in the United States demonstrated antibiotic activity in culture fluids obtained from certain soil bacteria and in 1942 Waksman announced the first of a series of antibiotics to be isolated in his laboratory from various actinomycetes.

It is of interest to recall that in 1922 Fleming noted that a bacteriocidal substance which he named "lysozyme" was present in the tissues and secretions of animals and in egg white. This substance was later studied as a possible chemotherapeutic agent by Florey and his associates but was found to have little activity in vivo. Fortunately, their studies on penicillin proved more fruitful and the successful clinical trials with this substance in 1941, together with the stimulus provided by the demands of war, led to a rapid development of this newest field of chemotherapy.

Antibiotics are highly selective in their action; hence the nature of the infective organism should always be determined in order that the most effective antibiotic may be used. It is also essential that the antibiotic be administered in adequate dosage since resistant strains may develop during the course of therapy if submaximal doses are used. There is considerable variation in the ability of various strains and species of micro-organisms to develop resistance to antibiotics as well as variation among the antibiotics concerning their ability to foster the development of such resistant strains. This is illustrated by the data in Table 8. After thirty transfers into media containing progressively higher concentrations of the antibiotic, a strain of gonococcus increased its resistance to a point where the bacteria could tolerate three hundred fifty times the original maximum tolerated concentration of penicillin. However, when streptomycin was used in place of penicillin, only

three or four transfers were necessary to increase the resistance of this strain to a point where the organisms grew in a saturated solution of the drug. Furthermore, the streptomycin-resistant strains persisted for longer than 14 weeks and showed an enhanced virulence, while the penicillin-resistant strains were less virulent and soon reverted to their original sensitivity.

TABLE 8

ANTIBIOTIC ORGANISM	MAXIMUM CONCENTRATION (UNITS PER CC.) OF DRUG PERMITTING GROWTH BEFORE AND AFTER TRANSFERS IN DRUG-CONTAINING MEDIA		NUMBER OF TRANSFERS
	BEFORE		
	AFTER		
Penicillin	{ gonococcus meningococcus	0.06	21 36 41 5,000
		0.3	147 30 137 30
Streptomycin	{ gonococcus meningococcus	8-40	4
		1-40	3

From C. P. Miller: J.A.M.A. 130: 485, 1946, with subsequent data by personal communication.

The use of antibiotics as chemotherapeutic agents is of such recent origin that an impartial appraisal of their usefulness is not always possible. The low toxicity of penicillin and its effectiveness in certain infections unaffected by sulfonamides has made it a most valuable addition to therapeutics. Streptomycin and tyrothricin have as yet received less extensive use; but they appear to be of definite value, the former primarily in the treatment of diseases due to gram-negative organisms and the latter as a local anti-infective, while early clinical reports on bacitracin indicate that this antibiotic may be of special value in the treatment of penicillin- and sulfonamide-resistant surgical infections.

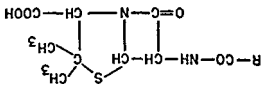
## PENICILLIN

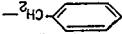
Penicillin is obtained commercially from the molds *Penicillium notatum* or *P. chrysogenum* by a variety of procedures. The rapid development of the large-scale production of penicillin is a tribute to the co-operative efforts of the English group of workers with a number of governmental, university and commercial laboratories in this country. This involved not only continued improvements in the technical aspects of production of this mold metabolite but also in the search for the most suitable strains of *Penicillium* and even the creation of new strains by artificial mutation to increase the yield of the drug.

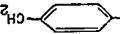
**Chemistry.** Penicillin is now known to exist in several forms which differ chemically in the side chains attached to the basic nuclear structure. These are identified in the United States as penicillin F, G, K and X. In Great Britain, penicillins F, G and X are known as penicillin I, II and III respectively. The four forms have approximately equal bacteriostatic activity when tested *in vitro*. However, penicillin K has very little chemotherapeutic activity *in vivo*. This is thought to be due to the greater adsorption of penicillin K on serum and tissue proteins, the adsorbed fraction being inactive against most, if not all, organisms. This inactivation by adsorption explains both the relative ineffectiveness of penicillin K *in vivo* and also the lower blood concentration obtained with a given dose of this penicillin type, since by biologic assay only the active penicillin is measured. Low recoveries may also be obtained in *in vitro* tests when serum or tissue proteins are added to the media. The recognition of the comparative inactivity *in vivo* of penicillin K has served to explain a number of disappointing results in penicillin therapy, since some of the earlier commercial preparations were shown to have contained appreciable amounts of this penicillin.

The penicillins are organic acids. On acid hydrolysis, they yield several degradation products, including a d-amino

acid, penicillamine or d-β-dimethylcysteine. Synthetic penicillins have been produced in minute yield by condensation of penicillamines with 2-benzyl-4-methoxymethylene-5(4)-oxazolone, while further compounds with antibiotic activity have been obtained by substituting other d-amino-β-mercapto acids for penicillamine. The constitutional formula of penicillin has not been fully established but it seems most probably to involve a β-lactam structure.



Penicillin F,  $\Delta^2$ -penicillin;  $\text{R} = \text{CH}_3-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$   
 Penicillin G, benzylpenicillin;  $\text{R} =$    $-\text{CH}_2-$

Penicillin X, *p*-hydroxybenzylpenicillin;  $\text{R} = \text{HO}-$    $-\text{CH}_2-$   
 Penicillin K, *N*-heptylpenicillin;  $\text{R} = \text{CH}_3-(\text{CH}_2)_5-\text{CH}_2-$

*Probable Basic Formulae of Penicillins.*

Crystalline preparations of penicillin are odorless and tasteless. Amorphous preparations are yellow and have a bitter taste, which may be objectionable when they are used locally in the mouth and throat. Only the solid crystalline form may be stored without refrigeration. Aqueous solutions of penicillin are unstable; however, they may be used as much as a month after preparation if they have been kept refrigerated and are sterile and neutral or slightly acid. Certain micro-organisms are capable of inactivating penicillin because of the presence of an enzyme, penicillinase. Penicillinase is of practical importance both in determining the therapeutic effectiveness of penicillin and in testing the sterility of commercial preparations of the drug. It permits



the selective destruction of penicillin in cultures of pharmaceutical preparations, or of infected fluids such as blood or pus from patients under treatment. This is a necessary prerequisite for demonstrating the absence of penicillin-sensitive micro-organisms since the organisms will not grow and hence cannot be detected in the presence of the drug. Furthermore, assay of the penicillinase content of infecting organisms may be of value in explaining or detecting penicillin-resistant forms of a usually sensitive species of bacteria.

**Metabolism.** The sensitivity of penicillin solutions to acid, coupled with the high content of penicillinase of the intestinal bacteria, produces erratic results when penicillin is given by mouth; hence, during the period when the use of penicillin was restricted, the drug was administered only parenterally. With abundant supplies now available, the convenience of the oral route has favored its more extensive use and a number of procedures have been utilized to improve the absorption of penicillin from the gastro-intestinal tract. Since penicillin is sensitive to alkaline solutions as well as to acid, simultaneous administration of sodium bicarbonate or similar alkaline agents is of no value in protecting the drug from destruction. However, approximately 20 per cent absorption may be obtained if the penicillin is given admixed with a buffering agent such as sodium or calcium citrate, magnesium hydroxide or an aluminum preparation. Some success has also been obtained with enteric-coated capsules and with penicillin-in-oil for oral use.

Maintenance of optimal blood concentration is advisable for adequate control of systemic infections. This requires frequent administration of the drug, since penicillin is rapidly excreted by the kidneys. Methods for continuous intravenous or intramuscular infusion have been devised and may be used in severe infections. The drug is, however, most often given intramuscularly in aqueous solution at

intervals of from 2 to 6 hours throughout the day and night. Recently, preparations of penicillin in peanut oil and bees-wax have been introduced for intramuscular or subcutaneous injections. These afford a convenient way of insuring an adequate blood concentration of the drug for from 12 to 24 hours with a single injection. Similarly, delayed absorption from intramuscular injections may be obtained by the local application of ice bags or by admixture of the penicillin with plasma proteins or with a vasoconstrictor such as epinephrine.

Penicillin may also be given by inhalation both for local and for systemic effects. When penicillin is administered as an aerosol, it is rapidly absorbed into the circulation to produce blood levels comparable with those obtained by intramuscular or intravenous administration.

Attempts have been made to decrease the rate of excretion of penicillin by the kidneys in order to obviate the necessity for frequent administration and to attain higher blood concentrations. Penicillin appears in the glomerular filtrate but the greater bulk (80 per cent) is secreted by the kidney tubules. This tubular excretion can be retarded by the administration of such substances as diodrast, para-aminohippuric acid, benzoic acid, sodium benzoate or caronamide. The use of adequate amounts of these substances will decrease the excretion rate to as little as one third of the ordinary rate. Renal excretion is also greatly reduced in nephritis and other forms of impaired renal function. Penicillin readily diffuses into the body fluids and tissues, with the exception of the cerebrospinal and synovial fluids, the humors of the eye, and probably also the pleural cavity. For the treatment of infections in those areas which are not easily reached by systemically administered penicillin its local injection may be necessary. This has been particularly successful in cases of empyema when the infecting organism is sulfonamide-resistant. In such cases, response to

intrapleural injections of penicillin is usually prompt, and since the drug does not readily diffuse out of the cavity, injections need only be made at 24- or 48-hour intervals.

While there is some evidence that penicillin can penetrate the cerebrospinal barrier in meningitis, intrathecal injections of penicillin are generally administered in this condition to insure adequate concentrations of the drug reaching the causative organisms. Such injections, however, may be accompanied by unusual toxic symptoms such as convulsions or syncope.

Penicillin finds wide use in the local treatment of boils and carbuncles and other localized infections when it can be injected directly into the diseased area. The drug is not rapidly lost by diffusion and local concentration remains high. Dramatic improvement can be expected in from 12 to 48 hours, or not at all.

**Activity.** The use of penicillin is especially effective in infections caused by grampositive organisms, including *Staphylococcus aureus* and *albus*, *Streptococcus hemolyticus* and *viridans*, pneumococci, clostridia and *Corynebacterium diphtheriae*. Gonococci and meningococci are also susceptible, but, in general, gram-negative forms are resistant to penicillin. Penicillin has given promising results in the treatment of early syphilis and because of its lack of toxicity is probably the method of choice for the short-term treatment of this disease. However, final evaluation of the results of penicillin treatment of syphilis must await the completion of long-term studies on the permanence of cure. Penicillin appears to be effective in other spirochetal diseases, such as Vincent's angina, yaws and probably also relapsing fever.

The average penicillin concentration required to inhibit bacterial growth in vitro may vary from 0.01 to 0.5 or more units per cc. In vivo, maximal results are usually obtained with blood concentrations of from 0.04 to 0.2

units per cc. Higher concentrations may be necessary in certain infections, particularly syphilis, diphtheria, gangrene and subacute bacterial endocarditis. The mechanism by which penicillin exerts its action is not understood. It is known to differ from that of the sulfonamides, hence cross-resistance is not to be expected. Penicillin is not markedly inhibited by the presence of blood, pus or the products of tissue degeneration, nor do the local anesthetic agents interfere with its action. It affords some degree of protection against meningococcus endotoxin, increases the requirements of the body for nicotinic acid, and has an inhibiting action on urease, although these actions are probably not directly related to its bacteriostatic and bacteriocidal activity.

Toxicity. Penicillin is the least toxic of the chemotherapeutic agents. Malaise with chills and fever and headache are rare and minor symptoms. Intramuscular or subcutaneous injection may be accompanied by local pain which, however, is preventable by the addition of a local anesthetic to the penicillin solution before injection. Allergic manifestations are usually present in about 10 per cent of the cases. They usually consist of rash, angioneurotic edema and very effective reactions in syphilitic patients inadequately pretreated with one of the slower-acting agents. Standardization of Penicillin. The international unit of pure sodium penicillin G. Assay is generally effected by comparing the growth inhibitory effects of the standard and unknown on a penicillin-sensitive organism. The international unit is defined as the amount of penicillin necessary to form a zone of inhibition 24 mm. in diameter in a culture of particular strains of *Staphylococcus aureus*.

## STREPTOMYCIN

Streptomycin is an antibiotic substance formed by certain strains of the fungus *Streptomyces griseus* in a suitable media. It was first isolated by Waksman in 1944 and is now available in crystalline form. It is usually dispensed in a relatively pure state as the hydrochloride or sulfate salt.

For systemic use, streptomycin must be administered parenterally, since it is not appreciably absorbed on oral administration. Intramuscular injection is safer and as effective as intravenous. Pain at the injection site may be minimized by the addition of procaine to the streptomycin solution.

Streptomycin is usually injected as a 10 per cent solution in isotonic saline or distilled water. The solution is relatively stable. The average dose is 0.4 Gm. of streptomycin repeated at 4-hour intervals.

Streptomycin is readily absorbed following intramuscular injection. It is apparently excreted by glomerular filtration only and not by tubular excretion and therefore remains in the blood stream for a longer period than penicillin. It does not diffuse readily into the cerebrospinal fluid.

Streptomycin is effective against a number of gram-negative organisms, including *Escherichia coli*, *Pasteurella tularensis*, *Hemophilus influenzae*, *Pseudomonas aeruginosa*, *Bacillus proteus*, *Eberthella typhosa* and *Brucella abortus* and *melitensis*. It appears to be of particular value in sulfonamide- and penicillin-resistant infections of the urinary tract and is the most effective chemotherapeutic agent available for the treatment of tularemia. Animal experiments have indicated its effectiveness in the treatment of tuberculosis and preliminary results in human beings have been encouraging.

If large doses of streptomycin are administered over a long period of time, symptoms of vestibular disturbance including dizziness, tinnitus and deafness may occur. Milder toxic symptoms, which may be due to impurities, include

skin rashes, joint and muscle pains and nausea and vomiting. A histamine-like reaction has been reported following streptomycin injection but this has been shown to be due to a contaminant. There is some evidence that renal irritation may occur with large doses.

Standardization of Streptomycin. Assays of streptomycin are based on the inhibition of growth of a standard strain of *E. coli* as determined by the dilution method. The official streptomycin unit ("S" unit) is defined as the activity of 1 microgram of pure crystalline streptomycin base.

## TYROTHRIN

Tyrothricin is a mixture of at least two antibiotic substances, gramicidin and tyrocidin. The former, though present in lesser amounts, is responsible for most of the activity of tyrothricin since tyrocidin is largely inhibited by the presence of serum proteins and cephalin. Tyrothricin was first isolated in 1939 by Dubos from the gram-positive soil organism *Bacillus brevis*. At that time he named the preparation gramicidin but altered this to tyrothricin the following year when he recognized the presence of more than one active agent.

Tyrothricin is effective against a variety of gram-positive organisms, including *Streptococcus hemolyticus*, *faecalis*, *pyogenes* and *Staphylococcus aureus*. However, its therapeutic usefulness is limited by its toxicity, parenteral administration causing hemolysis of the red blood cells. It is used largely for the local treatment of wounds, sinuses or superficial ulcers infected with gram-positive organisms. It has also been used in veterinary medicine for the treatment of bovine mastitis. The antibacterial activities of gramicidin and tyrocidin appear to be related to their detergent properties. The optimum therapeutic concentration appears to be approximately 500 micrograms per cc.

Recently, Gramacidin-S has been isolated from a *B. brevis* type of organism by a group of Russian workers. It appears

to be more effective on gram-negative organisms than gramicidin but equally as toxic. Gramicidin-S, gramicidin and tyrocidin are all polypeptides.

### BACITRACIN

Bacitracin is an antibiotic isolated by Johnson, Anker and Meleney in 1943 from a strain of the *B. subtilis* group of organisms. It received its name because the bacillus was isolated from a compound fracture in the leg of a young patient named Margaret Tracey. In vitro experiments indicated that it possessed bacteriocidal action largely against gram-positive organisms, though gonococci and meningococci were also susceptible. In vivo, it proved active against hemolytic streptococcal infections in mice and gas-gangrene infections in guinea pigs.

Bacitracin has had as yet limited clinical trial. Recently, Meleney and Johnson have reported its effectiveness in a number of surgical infections which were resistant to penicillin and sulfonamides. It is apparently nontoxic and non-irritating when applied locally and its action is not inhibited by the presence of pus or micro-organisms. It is now being produced commercially so that further clinical studies will be forthcoming.

Subtilin, another antibiotic obtained from the *B. subtilis* group, was isolated by Jansen and Hirshmann in 1944. In addition to its in vitro activity against a number of bacteria, it has recently been shown to be active in vitro against *Endameba histolytica*, *Trypanosoma equiperdum* and *Leishmania donovani*. Its activity is apparently due, at least in part, to its detergent properties.

### MISCELLANEOUS ANTIBIOTICS

A number of other antibiotic substances have been tested for their therapeutic value. Some of these, such as pyocyanine and pyocyanase obtained from *Pseudomonas pyocya-*

*neq*, actinomycin A and B from *Actinomyces antibioticus*, gliotoxin from *Trichoderma lignorum*, fumagatin from *Aspergillus fumigatus*, citrinin from *Penicillium citrinum* and streptothricin from *Actinomyces lavendulae*, are too toxic to be of practical importance. Patulin, obtained from *Penicillium patulum*, enjoyed brief popularity as an alleged cure for the common cold, but well-controlled experiments showed the early claims to be unfounded. It is apparently identical with claviform obtained from *P. claviform* and clavacin from *Aspergillus clavatus* and is too toxic for parenteral use.

## PREPARATIONS

Penicillin calcium U.S.P.; B.P.

Penicillin sodium U.S.P.; B.P.

Penicillin dental cones U.S.P. Usually contain 1,000 and 5,000 units of penicillin, with or without a sulfonamide preparation.

Injection of penicillin B.P.

Penicillin injection in oil and wax U.S.P.; B.P. Contains 100,000, 200,000 and 300,000 units per cc.

Penicillin ointment U.S.P.; B.P. B.P. preparation contains 500 units per Gm.

Penicillin ointment for the eye B.P. Contains 1,000 units per Gm.

Sterilized penicillin cream B.P.; penicillin cream B.P. Contains 500 units per Gm.

Penicillin tablets U.S.P. Usually 20,000 and 25,000 unit tablets.

Penicillin troches U.S.P.; B.P. Usually contain 500, 1,000 and 20,000 units

Tablets buffered penicillin N.N.R.

Streptomycin N.N.R.

Tyrothricin N.N.R.



## BIBLIOGRAPHY

## GENERAL

- Kolmer, John A.: *Penicillin Therapy, Including Tyrothricin and Other Antibiotic Therapy*, New York, Appleton-Century, 1947.
- Herrell, W. L.: *Penicillin and Other Antibiotic Agents*, ed. 2, Philadelphia, Saunders, 1947.
- Waksman, S. A.: Production and nature of antibiotic substances, *Harvey Lect.* 40:77, 1944-1945.
- Dubos, R. J.: Utilization of selective microbial agents in the study of biological problems, *Harvey Lect.* 35:223, 1939-1940.

## PENICILLIN

- Abraham, E. P., E. Chain, C. M. Fletcher, A. D. Gardner, N. G. Heatley, M. A. Jennings and H. W. Florey: Further observations on penicillin, *Lancet* 2:177, 1941.
- Beyer, K. H., W. F. Verwey, R. Woodward, L. Peters and P. A. Mattis: The enhancement of the plasma concentration of penicillin in dogs by the simultaneous administration of para-aminohippuric acid, III, *Am. J. M. Sc.* 209:608, 1945.
- Chain, E., H. W. Florey, A. D. Gardner, N. G. Heatley, M. A. Jennings, J. Orr-Ewing and A. G. Sanders: Penicillin as a chemotherapeutic agent, *Lancet* 239:226, 1940.
- Eagle, H.: The therapeutic activity of penicillins F, G, K and X in experimental infections with pneumococcus Type I and *Streptococcus pyogenes*, *J. Exper. Med.* 85:175, 1947.
- Fleming, Sir Alexander: *Penicillin, Its Practical Application*, Philadelphia, Blakiston, 1946.
- Goerner, J. R., A. J. Geiger and F. G. Blake: Treatment of subacute bacterial endocarditis with penicillin: report of cases treated without anticoagulant agents, *Ann. Int. Med.* 23:491, 1945.
- Heller, Jr., J. R.: Results of rapid treatment of early syphilis, *J.A.M.A.* 132:258, 1946.
- Levy, II, L., and N. McKrill: Results in the treatment of subacute bacterial endocarditis, *Arch. Int. Med.* 77:367, 1946.

- Meleney, F. L.: Penicillin in the treatment of established surgical infections—a systematic study of 744 including 82 septicemias, *Ann. Surg.* 124: 962, 1946.
- Mendell, T. H., and P. H. Prose: Severe allergic reactions to penicillin, *Am. J. M. Sc.* 212: 541, 1946.
- Morginson, W. J.: Toxic reactions accompanying penicillin therapy, *J.A.M.A.* 132: 915, 1946.
- Rake, Geoffrey, and A. P. Richardson: Pharmacology of penicillin, *Ann. New York Acad. Sc.* 48: 143, 1946.
- Richardson, A. P., I. Miller, C. Schumacher, W. Jambo, F. Pansy and D. Lapedes: Physiological disposition of penicillin G and K in dogs, *Proc. Soc. Exper. Biol. & Med.* 63: 514, 1946.
- du Vigneaud, V., F. H. Carpenter, R. W. Holley, A. H. Livermore and J. R. Rochele: Synthetic penicillin, *Science* 104: 431, 1946.
- Walker, A. E., and H. C. Johnson: Penicillin in Neurosurgery, Springfield, Ill., Thomas, 1946.
- Walker, A. E., and H. C. Johnson: The chemical study of penicillin, *Science* 105: 653, 1947.
- Walker, A. E., and H. C. Johnson: The changing character of commercial penicillin—with suggestions as to the use of penicillin in syphilis, *J.A.M.A.* 131: 271, 1946.
- Adcock, J. D., and R. A. Hettig: Absorption, distribution and excretion of streptomycin, *Arch. Int. Med.* 77: 179, 1946.
- Farrington, R. F., H. Hull-Smith, P. A. Bunn, and W. McDermott: Streptomycin toxicity, reactions to highly purified drug on long-continued administration to human subjects, *J.A.M.A.* 134: 679, 1947.
- Hinschaw, H. C., W. H. Feldman and K. H. Pfuetze: Treatment of tuberculosis with streptomycin—a summary of observations on one hundred cases, *J.A.M.A.* 132: 778, 1946.
- Miller, C. P., and M. Bohnhoff: Streptomycin resistance of gonococci and meningococci, *J.A.M.A.* 130: 485, 1946.
- Miller, C. P., and M. Bohnhoff: Development of streptomycin-resistant variants of meningococcus, *Science* 105: 620, 1947.

Pulaski, E. J.: Streptomycin in surgical infections: II. Infections of the genito-urinary tract, *Ann. Surg.* 124: 392, 1946.

Reimann, H. A., A. H. Price and W. F. Elias: Streptomycin for certain systemic infections and its effect on the urinary and fecal flora, *Arch. Int. Med.* 76:269, 1945.

Waksman, S. A., and A. Schatz: Streptomycin—origin, nature, and properties, *J. Am. Pharm. A.* 34:273, 1945.

#### TYROTHRICIN

Franks, A. G., W. L. Dobes and J. Jones: Tyrothricin in treatment of disease of skin, *Arch. Dermat. & Syph.* 53:498, 1946.

Gause, G. F., and M. G. Brazhnikova: Gramicidin S, origin and mode of action, *Lancet* 2:715, 1944.

Henderson, J.: The status of tyrothricin as an antibiotic agent for topical application, *J. Am. Pharm. A., Sc. Ed.* 35:141, 1946.

#### BACITRACIN

Anderson, H. H., G. G. Villjela, E. L. Hansen and R. K. Reed: Some physical and biologic properties of subtilin and other antibiotics, *Science* 103:419, 1946.

Johnson, B. A., H. Anker and F. L. Meleny: Bacitracin: a new antibiotic produced by a member of the *B. subtilis* group, *Science* 102:376, 1945.

Meleny, F. L., and B. Johnson: Bacitracin therapy—the first hundred cases of surgical infections treated locally with the antibiotic, *J.A.M.A.* 133:675, 1947.

# Miscellaneous Chemotherapeutic Agents

ANTIMONY COMPOUNDS	PARA-AMINOBENZOIC ACID
GOLD COMPOUNDS	CHAVULMOOCRA OIL
MELARSEN OXIDE	SULFONES
SURAMIN	MANDelic ACID AND
CYANINE DYES	METHENAMINE
DIAMIDINES	VACCINES AND SERA
PREPARATIONS	

## ANTIMONY COMPOUNDS

Organic antimony preparations are used in the treatment of schistosomiasis, filariasis, leishmaniasis and lymphogranuloma inguinale. They are of some value in the treatment of trypanosomiasis but are inferior to the arsenicals in this respect. Both trivalent and pentavalent antimonials are in use at the present time; inorganic antimony salts are not used therapeutically.

Potassium antimonyl tartrate (tartar emetic) and sodium antimonyl tartrate were first used in the treatment of schistosomiasis in 1915. Prior to their introduction emetine was the drug of choice in this condition but its use had proved far from satisfactory. The main disadvantage of the antimony tartrates lies in the fact that they must be given intravenously because of their irritant properties, and a course of treatment usually requires hospitalization with injections on alternate days for 3 weeks. Recently, an intensive 1- or 2-day treatment by continuous drip has given promising results.

Pulaski, E. J.: Streptomycin in surgical infections: II. Infections of the genito-urinary tract, *Ann. Surg.* 124: 392, 1946.

Reimann, H. A., A. H. Price and W. F. Elias: Streptomycin for certain systemic infections and its effect on the urinary and fecal flora, *Arch. Int. Med.* 76:269, 1945.

Waksman, S. A., and A. Schatz: Streptomycin—origin, nature, and properties, *J. Am. Pharm. A.* 34:273, 1945.

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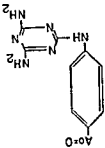
#### BACITRACIN

Anderson, H. H., G. G. Villela, E. L. Hansen and R. K. Reed: Some physical and biologic properties of subtilin and other antibiotics, *Science* 103:419, 1946.

Johnson, B. A., H. Anker and F. L. Meleny: Bacitracin: a new antibiotic produced by a member of the *B. subtilis* group, *Science* 102:376, 1945.

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# MELARSEN OXIDE



Melarsen oxide is a trivalent arsenical which, like the parent pentavalent compound, melarsen, has recently been shown to be effective in both early and late stages of African sleeping sickness. It is said to be much less toxic than

tryparsamide.

## SURAMIN

Suramin (naphuride, germanin, Bayer 205), a nonstaining complex urea derivative was introduced in Germany in 1920 for the treatment of trypanosomiasis. Its composition remained secret until 1924, when Fournau synthesized a compound of apparently identical chemical structure and therapeutic activity which he called moranyl or Fournau 309. It is of value only in the treatment of the early stages of the disease, being valueless after the central nervous system has become involved. For treatment of the late stages of sleeping sickness, tryparsamide remains the drug of choice.

Suramin forms a complex with plasma protein which greatly delays excretion of the drug from the body. Since the trypanocidal activity is not affected, a single dose of the drug will exert a chemotherapeutic effect for several months.

## CYANINE DYES

Certain cyanine dyes have recently been shown by Bieler and by Welch to exert a curative action on experimental filarial infections in rats. The adult worms are affected,

In 1929, the less toxic compound stibophen (fuadin, neo-antimosan) became available. This drug can be administered intramuscularly and injections can be given more frequently than those of the more toxic potassium or sodium antimonyl tartrate. Other trivalent antimonials include antimony thioglycollamide and the more soluble and somewhat less toxic antimony thioglycollate and anthiomaline or antimony lithium thiomalate. Pentavalent antimonials include stibosan ethylstibamine (neostibosan) and urea stibamine. While relatively less effective than the trivalent antimonials in the treatment of schistosomiasis, they have given promising results in the treatment of filariasis and leishmaniasis. In filariasis, the adult worm but not the microfilaria appears to be affected, hence treatment must be prolonged.

Characteristic toxic effects of antimonials include salivation, abdominal cramps, vomiting, a hard, unproductive cough, constriction of the chest, bradycardia, dizziness and collapse. There are often transient changes in the electrocardiogram, the most characteristic being a decrease in amplitude in the T wave.

### GOLD COMPOUNDS

Gold compounds are used in the treatment of Lupus erythematosus and of rheumatoid arthritis. They were formerly used in the treatment of pulmonary tuberculosis but proved of doubtful value and high toxicity. Gold sodium thiosulfate (sanocrysin) is probably the most widely used compound.

Gold compounds are administered intramuscularly or intravenously. They must be used cautiously because of their toxicity, manifestations of which include skin reactions, gastro-intestinal upsets, blood dyscrasias and liver and kidney damage. Small doses should be administered at first since many patients display an idiosyncrasy towards gold compounds.

**Toxicity.** Immediate but not dangerous effects of intravenous injection of the diamidines include a sharp fall in blood pressure, accompanied by breathlessness, tachycardia, dizziness and gastro-intestinal upsets. These effects can be minimized by slow injection or by the use of the more painful subcutaneous or intramuscular injections. Other effects occasionally noted include rigor, granulocytopenia and itching. Trigeminal-nerve neuritis has also been reported. It is supposedly due to toxic degeneration of the cells of the chief sensory nucleus in the pons.

Solutions of stilbamidine are unstable and contain toxic products of an unknown nature which give rise to a delayed form of poisoning characterized by nausea and vomiting followed by coma and death. In the solid form, stilbamidine is apparently quite stable.

## PARA-AMINOBENZOIC ACID

Para-aminobenzoic acid (PABA), a member of the vitamin B complex, has recently been shown to be effective in the treatment of a number of rickettsial diseases, including typhus fever, Rocky Mountain spotted fever and tsutsugamushi fever. It has been suggested that the drug stimulates the metabolism of the host cell, permitting it to overcome the invading organism. Sulfonamides appear to have a worsening effect in these conditions, due possibly to their suppression of the utilization of the naturally occurring para-aminobenzoic acid. Para-aminobenzoic acid is usually administered in a bicarbonate solution to minimize gastric upsets. Because of the rapid metabolism of the drug, frequent administration of large (from 2 to 8 Gm.) doses is necessary.

## CHAULMOOGRA OIL

Chaulmoogra oil (hydnocarpus oil) has been used for centuries in the treatment of leprosy, but authorities still



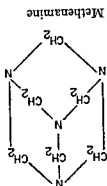
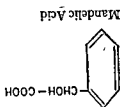
the preparations being active both in vivo and in vitro. The mode of action is suggested as being a depression of enzyme systems concerned with oxidative metabolism.

### DIAMIDINES

The guanidine derivatives synthalin and synthalin B were tried in 1926 and 1928 for the treatment of diabetes mellitus because of their blood-sugar-lowering power. In 1935 it was reported that these compounds were effective in experimental trypanosomiasis and since trypanosomes were known to require relatively large amounts of glucose to maintain their growth, it was assumed the protozoicidal action of these compounds was due to their effect on the blood sugar. Since these two compounds were too toxic for practical purposes, however, a further series of guanidines and diamidines were prepared and tested by Yorke and his colleagues. It was soon apparent that the chemotherapeutic activity of these compounds was quite unrelated to their action on the blood sugar. The most suitable compounds for clinical use include stilbamidine (4-4'-diamidino-stilbene), propamidine (4-4'-diamidine-diphenoxypropane) and pentamidine (4-4'-diamidine-diphenoxypentane). These substances are as effective as tryparsamide or suramin in early cases of *T. gambiense* infections and have the advantage of being much less toxic. They are apparently also effective as prophylactic agents. However, they are of little value in cases with central nervous system involvement. In the treatment of leishmaniasis, stilbamidine has been the most widely used of the diamidines.

The diamidines have a marked bacteriostatic effect in addition to their antiprotozoal activity. This activity is reported not to be inhibited by the presence of pus or body fluids. Propamidine has been used for the local treatment of infected wounds or burns. It apparently does not interfere with wound healing if used in 0.1 per cent concentration. It does not, however, affect *Proteus* or *Ps. pyocyanea*.

## MANDELIC ACID AND METHENAMINE



Mandelic acid and methenamine were formerly widely used as urinary antiseptics but have now been largely replaced by the sulfonamides and streptomycin. Both drugs are administered orally. Methenamine owes its activity to the liberation of formaldehyde, which occurs only in acid solution. Mandelic acid is also effective only in an acid medium; hence, if the urine is neutral or alkaline, acidifying agents such as ammonium chloride or nitrate should be administered concomitantly with these drugs.

## VACCINES AND SERA

A number of infectious diseases may be prevented or treated by biologic products which combat the invading organisms or their toxins by building up the immune reactions of the host. These include vaccines, which induce active immunity by stimulation of antibody formation by the host and serums, which confer passive immunity by their antibody content.

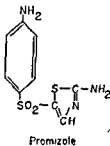
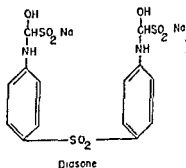
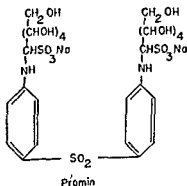
Vaccines are preparations of attenuated or dead bacteria or viruses or of bacterial toxins or toxoids. They include smallpox, rabies, cholera, plague, typhus and typhoid vaccines, diphtheria and scarlet-fever toxins and diphtheria and tetanus toxoids.

Serums include human immune globulin obtained from pooled human placental blood and placentae and used in

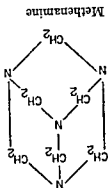
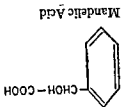
disagree as to its effectiveness. The active agents are thought to be the fatty acids known as chaulmoogric and hydno-carpic acids. Preparations are administered intramuscularly, since oral administration is usually accompanied by gastrointestinal upsets. While cures have been reported following its use, some observers have maintained these have been obtained only in mild cases which occasionally heal spontaneously.

## SULFONES

A number of sulfones, including promin, diasone and promizole, have given promising results in the treatment of experimental tuberculosis in the guinea pig. They have been tried clinically in the treatment of tuberculosis and of leprosy but their effects have been hard to evaluate because of the slow progress of these diseases. The drugs appear to be more toxic in man than in guinea pigs.



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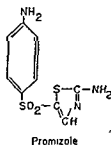
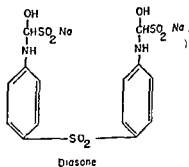
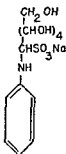
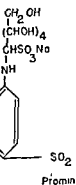
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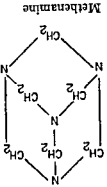
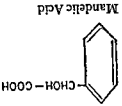
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Sera include human immune globulin obtained from pooled human placental blood and placenta and used in

the prevention and modification of measles; human measles and scarlet fever immune sera obtained from patients convalescing from measles and scarlet fever, respectively, and used in the prevention and treatment of these diseases; antibacterial sera, such as antipneumococcic and anti-meningococcic sera, which are obtained from the blood of immunized animals and which are believed to attack the pathogenic bacteria directly; and antitoxins, such as diphtheria, scarlet-fever, gas-gangrene and tetanus antitoxins, which are obtained from immunized animals and act by neutralizing the toxins of the invading organisms. Official preparations of vaccines and sera are listed at the end of this chapter. Details of dosage and administration may be obtained from the *United States Pharmacopoeia* or from *New and Nonofficial Remedies*, which also includes a number of nonofficial preparations.

The injection of foreign serum may result in an anaphylactoid or allergic reaction known as serum sickness. Signs and symptoms include urticaria, edema, joint pains, high fever and prostration. A more severe type of reaction develops in some patients who have previously received serum and who have developed a sensitivity or in patients who are naturally sensitive to a given serum. Immediate treatment includes the injection of epinephrine or of one of the antihistamine drugs. In some cases, desensitization can be accomplished by repeated injection of small doses of the serum.

### PREPARATIONS

Antimony potassium tartrate (tartar emetic) U.S.P.; B.P.  
0.03–0.12 Gm. intravenous.

Sodium antimonyltartrate B.P. 0.03–0.12 Gm. intravenous.

Antimony-sodium-thioglycolate injection U.S.P. 0.05–0.1 Gm. intramuscular or intravenous.

Stibophen B.P.; N.N.R. 0.054–0.32 Gm. intramuscular.

Ethylstibamine N.N.R. 0.05 Gm. intramuscular or intravenous.

Gold sodium thiosulfate N.N.R. 5-50 mg. intravenous or intramuscular.  
 Triphal N.N.R. Sodium aurothiobenzimidazole carboxylate. 5-75 mg. intravenous.

Suramin sodium U.S.P. 1 Gm. intravenous.

Mandelic acid N.N.R. 3 Gm.

Syrup of ammonium mandelate N.N.R.

Methenamine U.S.P. Hexamine B.P. 0.5 Gm.

Methenamine tablets U.S.P. Usually 0.3 and 0.5 Gm.

Cholera vaccine U.S.P.

Diphtheria and tetanus toxoids U.S.P.

Alum precipitated diphtheria and tetanus toxoids U.S.P.

Diphtheria antitoxin U.S.P.; B.P.

Diphtheria toxoid U.S.P.

Alum precipitated diphtheria toxoid U.S.P.

Diphtheria prophylactic B.P.

Bivalent gas-gangrene antitoxin U.S.P. Obtained from anti-

mals immunized against *Clostridium perfringens* and

*C. septicum* toxins.

Trivalent gas-gangrene antitoxin U.S.P. Obtained from anti-

mals immunized against *C. perfringens*, *C. septicum*, and

*C. oedematiens* (Novyi) toxins.

Pentavalent gas-gangrene antitoxin U.S.P. Obtained from

animals immunized against *C. perfringens*, *C. septicum*,

*C. oedematiens* (Novyi), *C. bifermentans* (Sordelli) and

*C. histolyticum* toxins.

Gas-gangrene antitoxin (oedematiens) B.P., gas-gangrene

antitoxin (perfringens) B.P., gas-gangrene antitoxin

(vibrio septique) B.P.

Human immune globulin U.S.P. A sterile solution of anti-

bodies obtained from human placental blood and placen-

tae pooled from at least ten healthy women.

Plague vaccine U.S.P.

Rabies vaccine U.S.P.

Scarlet fever streptococcus antitoxin U.S.P.

Scarlet fever streptococcus toxin U.S.P.



- Smallpox vaccine U.S.P. Vaccine lymph B.P.  
Tetanus and gas-gangrene antitoxins U.S.P. Obtained from animals immunized against *C. tetani*, *C. perfringens*, and *C. septicum* toxins.  
Tetanus antitoxin U.S.P.; B.P.  
Tetanus toxoid U.S.P.; B.P.  
Alum precipitated tetanus toxoid U.S.P.  
Typhoid and paratyphoid vaccine U.S.P.; B.P.  
Typhoid vaccine U.S.P.  
Epidemic typhus vaccine U.S.P.  
Yellow-fever vaccine U.S.P.

## BIBLIOGRAPHY

### ANTIMONIALS

- Brown, H. W., N. D. Thetford: Further studies on treatment of filariasis due to *wuchereria bancrofti* with lithium antimony thiomalate, *Am. J. Hyg.* 44:379, 1946.  
Brady, F. J., A. H. Lawton, D. B. Cowie, A. L. Andrews, A. T. Ness and G. E. Ogden: Localization of trivalent radioactive antimony following intravenous administration to dogs infected with *Dinofilaria immitis*, *Am. J. Trop. Med.* 25:103, 1945.  
Alves, W., and D. M. Blair: Schistosomiasis—intensive treatment with antimony, *Lancet* 1:9, 1946.  
Khalil, M., and M. H. Betache: Treatment of bilharziasis with a new compound "Fouadin"; report on 2041 cases, *Lancet* 1:234, 1930.  
Schroeder, E. F., F. A. Rose and H. Most: Effect of antimony on the electrocardiogram, *Am. J. M. Sc.* 212:679, 1946.

### GOLD

- Comroe, B. I.: The use and abuse of gold therapy in rheumatoid arthritis, *J.A.M.A.* 128:848, 1945.

### MELARSEN

- Weinman, D.: The treatment of African sleeping sickness with two new trivalent arsenical preparations (melarsen oxide and 70 A), *Am. J. Trop. Med.* 26:95, 1946.

## SURAMIN

Dewey, H. M., and A. Wornall: Studies on suramin Antypol; Bayer 205—5. The combination of the drug with the plasma and other proteins, *Biochem. J.* 40: 119, 1946.

## CYANINE DYES

Welch, A. D., L. Peters, E. Bueding, A. Valk, Jr., and A. Higashi: A new class of antihistaminic compounds, *Science* 105: 486, 1947.

## DIAMIDINES

Rosenberg, E. F.: The diamidines in chemotherapy: A survey of recent developments with a note regarding therapeutic trials in patients with rheumatoid arthritis, *Ann. Int. Med.* 25: 832, 1946.

Heathcote, R. St. A.: The diamidines: their pharmacological actions and their therapeutic uses in some tropical diseases, *J. Trop. Med. Hyg.* 49: 1, 33, 1946.

## PARA-AMINOBENZOIC ACID

Smith, P. K.: The use of para-aminobenzoic acid in endemic (murine) typhus, *J.A.M.A.* 131: 1114, 1946.

Flinn, L. B., J. W. Howard, C. W. Todd and E. G. Scott: Para-aminobenzoic acid treatment of Rocky Mountain spotted fever, *J.A.M.A.* 132: 911, 1946.

Greiff, D., H. Pinkerton and V. Moragues: Effect of enzyme inhibitors and activators on the multiplication of typhus rickettsiae: 1. Penicillin, para-aminobenzoic acid, sodium fluoride, and vitamins of the B group, *J. Exper. Med.* 80: 561, 1944.

McCoy, G. W.: Chaulmoogra oil in the treatment of leprosy, *Pub. Health Rep.* 57: 1727, 1942.

Tierney, N. A.: Effect of para-aminobenzoic acid in tsutsugamushi disease, *J.A.M.A.* 131: 280, 1946.

## VACCINES AND SERA

Derow, M. A., and S. B. Hooker: Active immunization against some common communicable diseases, *M. Clin. North America* 29: 1238, 1945.

Kolmer, J. A., and L. Tuft: *Clinical Immunology, Biotherapy and Chemotherapy*, Philadelphia, Saunders, 1942.

Parish, H. J.: A half-century of serology, *Proc. Roy Soc. Med.* 38: 1, 1944.



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